Clinical Study Protocol

A phase 1, dose blocked-randomized, double-blind, placebo controlled, single dosing, dose-escalation study to investigate the safety, tolerability, pharmacokinetic characteristics of hzVSF-v13 after intravenous(IV) administration in healthy male subjects

Investigational Product:

hzVSF-v13

Study No.: IM_hzVSF_v13-0001

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SIGNATURE PAGE

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Study No.: IM_hzVSF_v13-0001

Document Creator Mu Seong Ban

Signature _____ Date _____

Name In Jin Jang

Principal Investigator

Signature _____ Date _____

Name Yoon Won Kim, CEO

Sponsor ImmuneMed Inc.

SYNOPSIS

Title	A phase 1, dose blocked-randomized, double-blind, placebo controlled, single dosing, dose-escalation study to investigate the safety, tolerability, pharmacokinetic characteristics of hzVSF-v13 after intravenous(IV) administration in healthy male subjects
Objective	· To evaluate the safety and tolerability after intravenous administration of a single dose of the study drug hzVSF-v13 in healthy male subjects. · To evaluate the pharmacokinetic characteristics after intravenous administration of a single dose of the study drug hzVSF-v13 in healthy male subjects.
Principal Investigator	Professor In Jin Jang, M.D., Ph.D.
Study Site	Seoul National University College of Medicine/Department of Clinical Pharmacology and Therapeutics, Seoul National University Hospital
Sponsor	ImmuneMed Inc.
Analytical Testing Institution	APACE Co., Ltd. (pharmacokinetics) Hallym University College of Medicine Laboratory (immunogenicity)
Expected Target Disease	Influenza, hepatitis B and C
Investigational Product	• hzVSF-v13 • Placebo
Clinical Study Phase	Phase 1
Number of Subjects	● Number of Subjects 56 subjects in total hzVSF-v13 IV 10 mg, 20 mg – 4 subjects in each dose group (3 subjects for the study drug, 1 subject for the placebo) hzVSF-v13 IV 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, 1,200 mg – 8 subjects in each dose group (6 subjects for the study drug, 2 subject for the placebo)

- Single-dose study (intravenous administration)

Dose Group	Number of Subjects
Group 1 (10 mg IV)	hzVSF-v13: 3 subjects Placebo: 1 subject
Group 2 (20 mg IV)	hzVSF-v13: 3 subjects Placebo: 1 subject
Group 3 (50 mg IV)	hzVSF-v13: 6 subjects Placebo: 2 subjects
Group 4 (100 mg IV)	hzVSF-v13: 6 subjects Placebo: 2 subjects
Group 5 (200 mg IV)	hzVSF-v13: 6 subjects Placebo: 2 subjects
Group 6 (400 mg IV)	hzVSF-v13: 6 subjects Placebo: 2 subjects
Group 7 (800 mg IV)	hzVSF-v13: 6 subjects Placebo: 2 subjects
Group 8 (1200 mg IV)	hzVSF-v13: 6 subjects Placebo: 2 subjects

• Rationale for Calculation of the Number of Subjects

The purpose of the study is exploratory which is not to verify statistical hypotheses, and in the case of Phase 1 clinical studies being conducted using new drugs for which safety is not established, it is ethically desirable to conduct the study in the minimum number of subjects while satisfying the study objectives. In addition, dose groups had a certain ratio of subjects who will receive the placebo to enable double-blind for an objective safety and tolerability review. In this study, for the low dose groups (Groups 1 and 2), the sentinel dose groups, the target number of subjects per dose group has been set to 4 subjects per dose group, and the target number of subjects for other dose groups has been set to 8 subjects per dose group.

Inclusion/Exclusion Criteria

• **Inclusion Criteria**

1) Healthy males aged 19 to 45 years inclusive at the time of the screening visit
2) Individuals with a BMI of not less than 18.0 kg/m^2 to not more than 27.0 kg/m^2 and

weighed not less than 55 kg and less than 90 kg at the time of the screening visit

3) Individuals confirmed clinically healthy based on medical history, physical examination, vital sign, electrocardiography (ECG), and appropriate clinical laboratory tests (provided that individuals outside the normal range may participate subject to investigator discretion)
4) Individuals who have agreed to use a medically acceptable method of dual contraception and not to donate sperm from the first day until 30 days after the last day of investigational product administration
5) Individuals who have voluntarily decided to participate in this clinical study and have given a written consent to comply with the requirements of the clinical study

- **Exclusion Criteria**

1) Individuals with a clinically significant hepatic, renal, digestive, respiratory, musculoskeletal, endocrine, neuropsychological, hemato-oncologic, cardiovascular, or other disease or history
2) Individuals with a clinically significant history of hypersensitivity reactions to the components of hzVSF-v13, drugs containing components of the same class, or other drugs (aspirin, non-steroidal anti-inflammatory drugs, antibiotics, etc.)
3) Individuals with a positive result in the immunogenicity test for hzVSF-v13 conducted during the screening test
4) Individuals who have a history of drug abuse, or who have positive in the test for abuse-likely drugs in the urine drug screening test
5) Individuals with abnormal results for any of the following vital signs at the time of the screening visit:
   A. Systolic blood pressure: < 90 mmHg or > 140 mmHg
   B. Diastolic blood pressure: < 50 mmHg or > 90 mmHg
   C. Heart rate: < 50 bpm or > 90 bpm
6) Individuals with abnormal results for any of the following ECG items at the time of the screening visit:
   A. PR > 210 msec
   B. QRS complex: > 120 msec
   C. QTc > 450 msec

7) Individuals who have participated in another clinical study or bioequivalence study and received an investigational product within 3 months prior to the first day of administration (provided that 6 months from 06/12/2019)
8) Individuals who have donated whole blood within 2 months prior to the first day of administration, or donated blood components or received blood within 1 month prior to the first day of administration
9) Individuals who have taken drug-metabolizing enzyme inducers or inhibitors, such as barbitals, within 1 month prior to the screening
10) Individuals who have consumed grapefruit/caffeine-containing foods within 3 days of the first administration, and individuals who are unable to avoid consuming grapefruit-containing foods from 3 days prior to admission until the date of discharge
11) Individuals who have taken prescription drugs or oriental medications within 2 weeks prior to the first day of administration, or who have taken over-the-counter (OTC) drugs within 1 week prior to the first day of administration (provided that individuals who meet other requirements may participate in the clinical study subject to investigator discretion)
12) Individuals who consume high amounts of caffeine or alcohol and individuals who are heavy smokers (caffeine > 5 units/day, alcohol > 21 units/week (1 unit = 10 mL of pure alcohol), smoking > 10 cigarettes/day)
13) Individuals who are unable to eat meals provided by the study site
14) Individuals who have participated in this study
15) Individuals who have a positive result for serology (hepatitis B, human immunodeficiency virus [HIV], and hepatitis C tests)
16) Individuals with veins that are not suitable for intravenous catheter insertion or multiple venipunctures
17) Individuals who do not agree to use a medically acceptable method of dual contraception from the first day until 30 days after the last day of investigational product administration
18) Other individuals deemed unsuitable as a subject by an investigator

- **Withdrawal Criteria**

1) In the case that a subject requests discontinuation of the investigational product

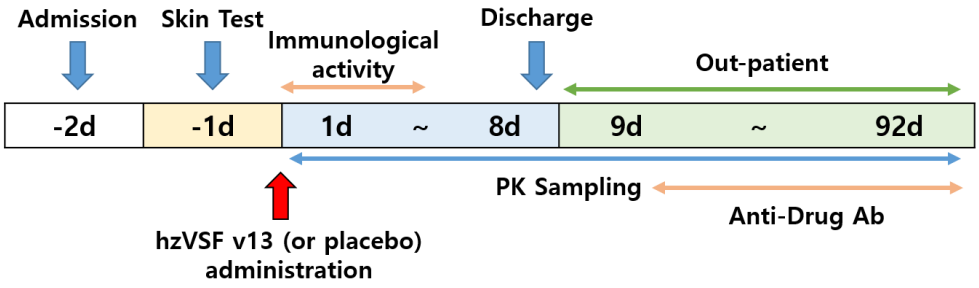
	administration during the clinical study, or withdraws his consent to participation in the study 2) In the case that a subject has received a drug that is expected to affect the evaluation of the safety or pharmacokinetics of the study drug during the clinical study 3) In the case that serious adverse events/adverse drug reactions have occurred 4) In the case that a subject is unable to perform blood sampling for the testing for pharmacokinetics/safety 5) In the case that significant protocol violation cases have been newly identified during the clinical study 6) In the case that the sponsor or the Ministry of Food and Drug Safety requests discontinuation 7) In the case that the principal investigator/investigator determines that the study has to be discontinued due to other reasons
Analytical Procedure	This is a Phase 1, dose blocked-randomized, double-blind, placebo controlled, single dosing, dose-escalation study to investigate the safety, tolerability, pharmacokinetic characteristics of hzVSF-v13 after intravenous administration in healthy male subjects. Each dose group will have hzVSF-v13 and the placebo randomized at a 3:1 ratio to conduct the clinical study. The study will be proceeded sequentially from the lowest dose, and whether to proceed with the next dose will be determined based on the tolerability and safety results of the previous dose. Each subject in Group 1 and Group 2 will be administered, and if no significant dose-limiting toxicity (DLT) occurs within 72 hours, the next subject will be administered. In the case of all dose groups except for Group 1 and Group 2 (Group 3–Group 8), 3 out of 8 subjects in each dose group (2 subjects for the study drug and 1 subject for the placebo) will receive the investigational product (hzVSF-v13 or placebo) at least 72 hours earlier than the remaining subjects in the same dose group. If no significant dose-limiting toxicity occurs within 72 hours, the remaining subjects in the relevant dose group will receive the investigational product (hzVSF-v13 or placebo) depending on the randomization. In the case that at least 3 subjects experience a Grade 3 adverse event or at least 1 subject in certain dose groups experience a Grade 4 adverse event based on the Common Terminology

Criteria for Adverse Events (CTCAE) published by the United States National Cancer Institute (NCI), the principal investigator shall consult the Safety Monitoring Committee (SMC) and discuss discontinuation of the relevant dose group and dose escalation with the sponsor. (For Group 1 and Group 2, discontinuation of the dose group and dose escalation shall be considered based on the following criterion: occurrence of Grade 3 adverse event in at least 2 subjects or Grade 4 adverse event in at least 1 subject.)

The screening tests shall only be performed in volunteers within 4 weeks prior to the first day (1 d) of investigational product administration (−28 d to −2 d) in order to select the subjects considered to be eligible for this clinical study.

◆ **Single-Dose Study (Intravenous Administration)**

- 10 mg, 20 mg, 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, 1,200 mg IV



The selected subjects will be admitted to the Seoul National University Hospital Clinical Trials Center 2 days (-2d) prior to administration of the investigational product. The skin test will be performed a day (-1d) prior to administration of the investigational product. Only the subjects who did not have clinically significant findings in the skin test will have intravenous (IV) administration of the investigational product (hzVSF-v13 or placebo) at 9 a.m. on the day (1d) of investigational product administration. The subjects will be required to perform the clinical study procedures in accordance with the predefined schedule and will be discharged 7 days (8d) after the administration. Thereafter, the subjects will visit the Seoul National University Hospital Clinical Trial Center as outpatients from 9 d to 92 d in order to perform the clinical study procedures according to the predefined schedule. After completing all scheduled tests up to 15 d for each dose group, an independent SMC, established separately from this study, will evaluate the safety-related data. With reference to the evaluation result of the SMC, the principal investigator and the sponsor will decide

	by mutual consent whether to continue the clinical study and to proceed with the next step.
Evaluation Items	■ **Safety and Tolerability Assessments** - Monitoring of adverse events, such as subject and objective symptom - Physical examination - Vital signs - Electrocardiography (12-lead ECG) - Clinical laboratory tests - Immunogenicity test ■ **Pharmacokinetic Assessment** Blood samples will be collected to assess the pharmacokinetics of hzVSF-v13 until 2,184 hours after administration of the investigational product. - Blood collection time: 1 d 0 h (pre-dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 24 (2 d 0 h), 36 (2 d 12 h), 48 (3 d 0 h), 60 (3 d 12 h), 72 (4 d 0 h), 96 (5 d 0 h), 120 (6 d 0 h), 144 (7 d 0 h), 168 (8 d 0 h), 336 (15 d 0 h), 504 (22 d 0 h), 672 (29 d 0 h), 840 (36 d 0 h), 1,176 (50 d 0 h), 1,512 (64 d 0 h), 1,848 (78 d 0 h) and 2,184 h (92 d 0 h; post-dose). - Endpoints: C_{max}, AUC_{last}, AUC_{inf}, T_{max}, $t_{1/2}$, CL (or CL/F), and V_d (or V_d/F) ■ **Immunogenicity Test** Immunogenicity will be evaluated by confirming the production of antibodies against hzVSF-v13. - Blood collection time: Screening, 168 (8 d 0 h), 336 (15 d 0 h), 672 (29 d 0 h), 1,344 (57 d 0 h) and 2,184 h (92 d 0 h; post-dose).
Data Analysis	• **Demographic Data Analysis** Descriptive statistics (mean, standard deviation, etc.) will be obtained for all subjects and each dose group for basic demographic information of subjects, such as age, height, and weight.

	• **Pharmacokinetic Analysis** Pharmacokinetic variables will be obtained through a noncompartmental method using an appropriate and verified pharmacokinetics software (e.g., Phoenix WinNonlin® [Version 6.3 or higher; Pharsight, CA, USA]), and descriptive statistics (mean, standard deviation, median, maximum, minimum, etc.) will be obtained for each dose group. • **Safety Analysis** Adverse events will be tabulated for each dose group based on severity and causal relationship to the investigational product, and the frequency and percentage of subjects who experienced adverse events will be compared and evaluated. The results of vital sign, electrocardiography, clinical laboratory tests, and immunogenicity test will be reviewed comprehensively, and statistical analysis will be done as needed for the items that are considered clinically significant.

SUMMARY OF CLINICAL STUDY SCHEDULE

Schedule	Screening	Hospitalization period					Outpatient period
Item \ Day (d)	-28 ~ -2	-2	-1	1	2 ~ 7	8	9 ~ 92
Obtaining a written consent	●						
Checking demographic information/medical history	●						
Serology[1]	●						
Urine drug test[2]	●						
Checking the inclusion/exclusion criteria	●						
Assigning the randomization/subject numbers[3]			●				
Admission[4]		●					
Discharge[5]						●	
Skin test[6]			●				
Administration of the investigational product[7]				●			
Physical examination[8]	●			●		●	●
Vital signs[9]	●			●	●	●	●
Electrocardiography (12-lead ECG)[10]	●			●		●	●
Clinical laboratory tests[11]	●			●	●	●	●
Blood collection for pharmacokinetics[12]				●	●	●	●
Immunogenicity test[13]	●					●	●
Monitoring of adverse events		●	●	●	●	●	●
Checking on the concomitant medications	●	●	●	●	●	●	●
Tolerability/safety assessments[14]							●

[1] Serology: Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) tests shall be performed only at the screening.
[2] Urine drug test: It shall be performed only at the screening (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates).
[3] Assigning the randomization/subject numbers: The randomization and subject numbers shall be assigned after the skin test at −1 d.
[4] Admission: Subjects shall be admitted in the afternoon at −2 d.
[5] Discharge: Subjects shall be discharged after completing all scheduled tasks in the morning at 8 d.
[6] Skin test: The skin test shall be performed at −1 d.
[7] Administration of the investigational product: hzVSF-v13 (or the placebo) shall be administered intravenously at 9 a.m. at 1 d.
[8] Physical examination: It shall be performed at the screening, 1 d 0 h (pre-dose), 168 (8 d 0 h), 336 (15 d 0 h), 504 (22 d 0 h), 672 (29 d 0 h), 840 (36 d 0 h), 1,176 (50 d 0 h), 1,512 (64 d 0 h), 1,848 (78 d 0 h) and 2,184 h (92 d 0 h; post-dose).
[9] Vital signs: It shall be performed at the screening, 1 d 0 h (pre-dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 24 (2 d 0 h), 36 (2 d 12 h), 48 (3 d 0 h), 60 (3 d 12 h), 72 (4 d 0 h), 96 (5 d 0 h), 120 (6 d 0 h), 144 (7 d 0 h), 168 (8 d 0 h), 336 (15 d 0 h), 504 (22 d 0 h), 672 (29 d 0 h), 840 (36 d 0 h), 1,176 (50 d 0 h), 1,512 (64 d 0 h), 1,848 (78 d 0 h) and 2,184 h (92 d 0 h; post-dose) (systolic blood pressure, diastolic blood pressure, pulse rate, and temperature).
[10] Electrocardiography (12-lead ECG): It shall be performed at the screening, 1 d 0 h (pre-dose), 168 (8 d 0 h), 336 (15 d 0 h), 504 (22 d 0 h), 672 (29 d 0 h), 840 (36 d 0 h), 1,176 (50 d 0 h), 1,512 (64 d 0 h), 1,848 (78 d 0 h) and 2,184 h (92 d 0 h; post-dose).
[11] Clinical laboratory tests: It shall be performed at the screening, 1 d 0 h (pre-dose), 24 (2 d 0 h), 72 (4 d 0 h), 168 (8 d 0 h), 336 (15 d 0 h), 504 (22 d 0 h), 672 (29 d 0 h), 840 (36 d 0 h), 1,176 (50 d 0 h), 1,512 (64 d 0 h), 1,848 (78 d 0 h) and 2,184 h (92 d 0 h; post-dose) (hematology, blood chemistry, and urinalysis).
[12] Blood collection for pharmacokinetics: It shall be performed at 1 d 0 h (pre-dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 24 (2 d 0 h), 36 (2 d 12 h), 48 (3 d 0 h), 60 (3 d 12 h), 72 (4 d 0 h), 96 (5 d 0 h), 120 (6 d 0 h), 144 (7 d 0 h), 168 (8 d 0 h), 336 (15 d 0 h), 504 (22 d 0 h), 672 (29 d 0 h), 840 (36 d 0 h), 1,176 (50 d 0 h), 1,512 (64 d 0 h), 1,848 (78 d 0 h) and 2,184 h (92 d 0 h; post-dose).
[13] Immunogenicity test: It shall be performed at the screening, 168 (8 d 0 h), 336 (15 d 0 h), 672 (29 d 0 h), 1,344 (57 d 0 h) and 2,184 h (92 d 0 h; post-dose).
[14] Tolerability/safety assessments: The tolerance and safety of the relevant dose group shall be evaluated after completing all scheduled tests up to 15 d in order to determine whether to proceed to the next dose group.

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ABBREVIATIONS AND DEFINITION OF TERMS

Dose Group	Groups based on doses of the study drug
Investigational product	The study drug and placebo used in this clinical study
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
anti-HCV Ab	Anti-hepatitis C virus antibody
anti-HIV Ab	Anti-human immunodeficiency virus antibody
AST	Aspartate transaminase
AUC_{last}	Area under the plasma drug concentration-time curve over the time interval from 0 to the last quantifiable plasma concentration Area under the blood concentration–time curve to the time of the last blood collection that can be measured, calculated using the trapezoidal rule. The interval of an increase in blood concentration is calculated using the linear trapezoidal method, and the interval of a decrease in blood concentration is calculated using the log–linear trapezoidal summation.
AUC_{inf}	Area under the plasma drug concentration-time curve over the time interval from 0 extrapolated to infinity Area under the blood concentration–time curve extrapolated to infinity after administration of a single dose. $AUC_{inf} = AUC_{last} + C_{last} / \lambda_z$
$AUC_{\tau,7d}$	Area under the blood concentration–time curve between dosing intervals after repeat-doses at 7 d
$t_{1/2}$	Terminal half-life
BP	Blood pressure
BUN	Blood urea nitrogen
$C_{av,7d}$	Average plasma concentration during a dosing interval at 7 day
C_{last}	Last concentration of drug in plasma Concentration in blood at the last blood collection time measurable
C_{max}	Maximum concentration of drug in plasma Maximum concentration in plasma/serum/blood

CL	Clearance of drug (mL/day/Kg)
CL/F	Apparent clearance
CPE	Cytopathic effect
CPK	Creatine phosphokinase
CRF	Case report form
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EMC	Encephalomyocarditis
EMC-D	D-variant of EMC virus
ECG	Electrocardiogram
γ-GT	Gamma-glutamyl transpeptidase
HBsAg	Hepatitis B virus surface antigen
hzVSF-v13	Humanized immunoglobulin of virus suppressing factor variant 13
HR	Heart rate
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
PR	Pulse rate
RBC	Red blood cell
SBP	Systolic blood pressure
SOP	Standard operating procedure
T_{max}	Time of maximum concentration Time to reach the maximum blood concentration after drug administration
V_d	Volume of distribution
WBC	White blood cell

1. TITLE AND PHASE OF THE CLINICAL STUDY

A phase 1, dose blocked-randomized, double-blind, placebo controlled, single dosing, dose-escalation study to investigate the safety, tolerability, pharmacokinetic characteristics of hzVSF-v13 after intravenous(IV) administration in healthy male subjects

A phase 1, dose blocked-randomized, double-blind, placebo controlled, single dosing, dose-escalation study to investigate the safety, tolerability, pharmacokinetic characteristics of hzVSF-v13 after intravenous(IV) administration in healthy male subjects

2. STUDY SITE AND ANALYSIS INSTITUTION

2.1. STUDY SITE

Seoul National University Hospital
Clinical Trials Center
101, Daehak-ro, Jongno-gu, Seoul, 03080, Korea

2.2. ANALYSIS INSTITUTION

Pharmacokinetic Analysis
APACE Co., Ltd.
#502, 101, Daehak-ro, Jongno-gu, Seoul, Korea
Convergence Research Building, Seoul National University College of Medicine, Yeongeon-dong

Immunogenicity Analysis
Hallym University College of Medicine Laboratory
#3603, Hallym University College of Medicine, 1, Hallymdaehak-gil, Chuncheon-si, Gangwon-do, Korea

3. NAME AND TITLE OF THE PRINCIPAL INVESTIGATOR, INVESTIGATORS, AND CO-INVESTIGATORS

3.1. PRINCIPAL INVESTIGATOR

Seoul National University College of Medicine/Department of Clinical Pharmacology and Therapeutics, Seoul National University Hospital
Professor In Jin Jang, MD, PhD

3.2. CO-INVESTIGATORS

Seoul National University College of Medicine/Department of Clinical Pharmacology and Therapeutics, Seoul National University Hospital
Professor Kyung Sang Yu, MD, PhD

Seoul National University College of Medicine/Department of Clinical Pharmacology and Therapeutics, Seoul National University Hospital
Associate Professor Joo Youn Cho, PhD

Seoul National University Hospital Clinical Trials Center/Department of Clinical Pharmacology and

Therapeutics, Seoul National University Hospital
Clinical Assistant Professor Seung Hwan Lee, MD, PhD

3.3. INVESTIGATORS

<See Attachment 3. Name and Title of investigators and Clinical Trial Pharmacists>

3.4. CLINICAL TRIAL PHARMACISTS

<See Attachment 3. Name and Title of investigators and Clinical Trial Pharmacists>

4. NAME AND ADDRESS OF THE SPONSOR

Sponsor: ImmuneMed Inc.

Address: #2-2, Bio-3, Chuncheon Bioindustry Foundation, Special Research Center, 32, Soyanggang-ro, Chuncheon-si, Gangwon-do, Korea

5. BACKGROUND OF THE CLINICAL STUDY

5.1. DETAILS OF THE DEVELOPMENT

Cells isolated from the spleen of mice infected with EMC virus were fused with cancer cells to obtain hybridoma cells, and then screened for substances with antiviral activity from these cells and selected. The substances secreted by these cells were named “VSF (virus suppressing factor)” derived from mice, and it was confirmed that VSF has antiviral activity against various viruses. Mouse-derived VSF has been humanized (hzVSF) with human immunoglobulin IgG4. The *in silico* method of Lonza was used to receive recommendation for thirteen variants of hzVSF-expected to have low immunogenicity. Among these, hzVSF-v13 has excellent antiviral activity and is unlikely to act as an immunogen in clinical because it does not cause T cell activity according to an *in vitro* peripheral blood mononuclear cells (PBMC) assay; therefore, it has been selected as a candidate substance. In addition, it is intended to be developed as a treatment of influenza virus by identifying the antiviral and anti-inflammatory activity in mice, ferrets and beagle dogs infected with influenza virus.

Also, it is intended to be developed as a treatment for hepatitis B and C because it has an excellent function to suppress proliferation of hepatitis B virus and hepatitis C virus.

5.2. EFFICACY PHARMACOLOGY TEST

Mice, ferrets, and beagle dogs were used for non-clinical efficacy evaluation. In the case of mice, 3 to 5 each of male and female mice were used for evaluation, and the doses were administered from 0.1 mg/kg to 2 mg/kg (1,000 U/kg to 20,000 U/kg). In the case of ferrets, 2 female ferrets per group were administered intravenously at 0.134 to 8.571 mg/kg 2 times, at 2 days and at 4 days after virus infection. In the case of beagle dogs, female dogs were administered a single dose of 0.5 mg/kg intravenously at 2 days after virus infection. In all laboratory animals administered, it was confirmed that influenza virus replication was suppressed and infiltration of immune cells into the lungs after influenza virus was suppressed by administration of hzVSF-v13. In the serum of mice, it was confirmed that the administration of hzVSF-v13 suppressed the production of inflammatory cytokines and inflammatory mediators.

In the cell experiment on hepatitis B virus and hepatitis C virus, it was confirmed that the synthesis of genes and proteins of not only cccDNA of hepatitis B virus but also viral proteins and 1a, 1b and 2a genotypes of hepatitis C virus was inhibited. In addition, in the cell experiment on mouse hepatitis virus which has similar pathology to human hepatitis, suppression of virus proliferation as well as suppression of growth,

suppression of inflammation, relief of symptoms and promotion of treatment were confirmed.

5.3. MECHANISM OF ACTION

hzVSF-v13 acts as a ligand for the mutated vimentin (VSF receptor, VR) that appears on the cell surface specifically in cells infected with virus, and it induces antiviral and anti-inflammatory mechanisms of action in cells. The binding site of the mutated vimentin to which hzVSF-v13 binds was confirmed, and it was confirmed that the antiviral action of hzVSF-v13 was absent in cells that do not express vimentin. In addition, in the case of cells expressed by introducing vimentin genes into the cells, antiviral ability against hzVSF-v13 process after virus infection was restored, whereas in the case of cells expressed by introducing mutated vimentin genes that do not bind to hzVSF-v13, cytotoxicity due to virus infection could not be suppressed even after hzVSF-v13 processing. Also, as a result of investigating the location in cells by binding fluorescence to hzVSF-v13 after virus infection, it was confirmed that hzVSF-v13 bound to mutated vimentin in the cell membrane on the cell surface and decomposed in lysosomes through endocytosis. It is considered that hzVSF-v13 processing in cells infected with EMC virus induces AKT protein phosphorylation which results in suppression of replication of the virus, whereas it inhibits NF-kB phosphorylation which results in suppression of inflammation.

5.4. SAFETY PHARMACOLOGY TEST

Evaluation of the effect on the cardiovascular system of anesthetic and unrestrained dogs by intravenous administration of hzVSF-v13: In this test, 4 male anesthetic and unrestrained beagle dogs with a remote transmitter inserted were administered the test substance hzVSF-v13 intravenously, and blood pressure and heart rate measurement and electrocardiography were performed to evaluate the effect on the cardiovascular system.

Dulbecco's phosphate buffered saline (DPBS) was an excipient administered as a reference substance for the first administration, and 6.25, 25 and 100 mg/kg doses of the test substance was administered for the second, third and fourth administration. The same animal received intravenous administration of a single dose of each dose at an interval of 1 week.

Cardiovascular parameters (blood pressure, heart rate and electrocardiogram) were assessed at 0 hours before initiation of the administration (pre-dose), and 0.083, 0.25, 0.5, 1, 2, 4, 6 and 24 hours after initiation of the administration.

Blood pressure (systolic, diastolic and mean blood pressure) and heart rate did not show any change by administration of 6.25 and 25 mg/kg doses of the test substance. In 1 case after administration of a 100 mg/kg dose of the test substance, blood pressure decreased and heart rate increased between 0.083 hours and 1 hour after initiation of the administration.

For electrocardiogram parameters (PR, QRS, QT and QTc intervals), the QRS, QT and QTc intervals were not influenced by administration of 6.25, 25 and 100 mg/kg doses of the test substance, but in 1 case after administration of a 100 mg/kg dose of the test substance, the PR interval showed a shortened trend compared to the reference substance administration at 0.25 hours to 2 hours after initiation of the administration.

Temperature did not show any change by administration of 6.25, 25 and 100 mg/kg doses of the test substance.

As a result of observation of general symptoms, vomiting was observed in 1 case after administration of a

100 mg/kg dose of the test substance.

From the above results, the test substance hzVSF-v13 was found to have no cardiovascular effect at 6.25 and 25 mg/kg doses when a single dose was administered intravenously to beagle dogs under this test condition. Decreased blood pressure, increased heart rate, and shortened PR interval were observed due to the effect of test substance administration in 1 case after administration of a 100 mg/kg dose, but they recovered within 24 hours after initiation of the administration.

5.5. PHARMACOKINETIC TEST

The concentration of hzVSF-v13 in the plasma was measured after intravenous administration of a single dose to mice in order to calculate toxicokinetic parameters. In the case of the systemic exposure level of hzVSF-v13, AUC was 78.8 μg•day/mL to 6,839.9 μg•day/mL, C_{max} was 5.2 μg/mL to 563.0 μg/mL, and $t_{1/2}$ was 8.9 to 10.1 days in male mice. In female mice, AUC was 113.0 μg•day/mL to 8,686.9 μg•day/mL, C_{max} was 5.5 μg/mL to 607.2 μg/mL, and $t_{1/2}$ was 10.2 to 13.4 days.

After intramuscular administration of a single dose of hzVSF to mice, they had a 6-week observation period. The administration concentrations were 0.2 mg/kg, 0.8 mg/kg and 3.2 mg/kg, blood samples were collected at 1, 2, 4, 7, 14, 21, 28 and 42 days during the observation period to measure the concentration of hzVSF in the plasma in order to calculate toxicokinetic parameters. In the case of the systemic exposure level of hzVSF-v13, AUC was 35.7 kg•day/mL to 906.7 kg•day/mL, C_{max} was 3.5 mg/mL to 60.7 mg/mL, and t1/2 was 6.4 to 8.0 days in male mice. In female mice, AUC was 32.4 kg•day/mL to 859.5 kg•day/mL, C_{max} was 3.6 mg/mL to 61.6 mg/mL, and t1/2 was 4.6 to 6.5 days. An increase in the blood concentration was observed in higher administration doses, and a decrease in the blood concentration was observed for the 6-week observation period thereafter. The systemic exposure level (C_{max}) increased at a ratio similar to the increase in administration dose, and it was determined that there was not much difference between the gender. In addition, cases of death and abnormal general symptoms were not observed.

As a result of measuring the concentration of hzVSF-v13 in the plasma after intravenous administration to rats for 2 week at 3 doses per week, 6 doses in total, and calculating toxicokinetic parameters, T_{max} was 14 to 14.02 days. For the systemic exposure level of hzVSF, the AUC_{all} and C_{max} were 4,095 ng•hr/mL to 59,151 ng•hr/mL and 307 ng/mL to 5,190 ng/mL in female animals. The AUC_{all} and C_{max} were 3,679 ng•hr/mL to 72,727 ng•hr/mL and 238 ng/mL to 6,153 ng/mL in female animals. In rats, the blood collection days in the 2-week administration period (administered 6 doses in total; administration days: Days 1, 3, 6, 9, 11 and 14) were Days 1, 6, 11, and 14, and an increase in the blood concentration was observed as the number of doses administered increased at all doses. The highest concentration was observed after the administration (0.5 hr) at the final administration day (Day 14) (excluding male low-dose group), and a decrease in the blood concentration was observed during the following 6-week observation period. The systemic exposure level (AUC_{all}, C_{max}) increased at a ratio similar to the increase in administration dose, and it is determined that there was no difference between the gender.

As a result of measuring the concentration of hzVSF-v13 in the plasma after intravenous administration to beagle dogs for 2 week at 3 doses per week, 6 doses in total, and calculating toxicokinetic parameters, T_{max} was 11.0 to 16.0 days. For the systemic exposure level of hzVSF-v13, the AUC_{all} and C_{max} were 2,842.1 μg•hr/mL to 62,769.4 μg•hr/mL and 276.0 μg/mL to 4,090.0 μg/mL in male animals. The AUC_{all} and C_{max} were 2,727.7 μg•hr/mL to 57,247.4 μg•hr/mL and 229.0 μg/mL to 4,180.0 μg/mL in female animals. In beagle dogs, the systemic exposure level (AUC_{all}, C_{max}) of the test substance hzVSF increased at a ratio similar to the increase in administration dose, and it increased according to the increase in the number of doses administered at all doses. The highest blood concentration (T_{max}) was observed at Day 11 (5th administration) in male animals in the 6.25 and 100 mg/kg treatment groups and female animals in the 6.25

and 25 mg/kg treatment groups, and at Day 14 (6th administration) and at 0.5 hr after the administration in male animals in the 25 mg/kg treatment group and female animals in the 100 mg/kg treatment group. Based on the results of analyses performed subsequently at every week up to weeks 3 to 8 (blood collection days: Days 22, 29, 36, 43, 50 and 57), blood concentration gradually decreased, and the test substance was detected up to week 8 in 1/2 male cases and up to week 7 in 1/2 female cases in the 100 mg/kg treatment group. In addition, differences between females and males were not observed. In addition, the half-life ($t_{1/2}$) after administering 6 doses for 2 weeks was 16.5 to 22.6 days at all doses in male and female animals.

5.6. TOXICITY TEST

- Single-dose toxicity test

• Single-intravenous-dose toxicity test of hzVSF-v13 using rats: This test was performed to evaluate the toxicity after intravenous administration of a single dose of the test substance hzVSF-v13 to 6-week-old male and female Sprague-Dawley rats, and to estimate the approximate lethal dose. The study was composed of 2 groups—a group treated with the test substance at a dose of 100 mg/kg and a control group (DPBS)—and a single dose was administered intravenously to 5 male and female animals respectively. For 14 days after the administration, general symptoms were observed and body weight was measured. Once the observation period was over, the animals were euthanized, and necropsy was performed. Cases of death were not observed in male and female animals in the 100 mg/kg treatment group. In addition, the effects of administration of the test substance on general symptoms, weight measurements, and necropsies were not recognized. Based on the results of intravenous administration of a single dose of hzVSF-v13 to rats under the conditions of this test, the approximate lethal dose has been determined to exceed 100 mg/kg in both male and female animals.

• Single-intramuscular-dose toxicity test of hzVSF-v13 using rats: This test was performed to evaluate the toxicity after intramuscular administration of a single dose of the test substance hzVSF-v13 to 6-week-old male and female Sprague-Dawley rats, and to estimate the approximate lethal dose. The study was composed of a group treated with the test substance at a dose of 80 mg/kg and a control group (DPBS), and a single dose was administered intramuscularly to 5 male and female animals respectively. For 14 days after the administration, general symptoms were observed and body weight was measured. Once the observation period was over, the animals were euthanized, and necropsy was performed. Cases of death and abnormal general symptoms were not observed in male and female animals in the 80 mg/kg treatment group. The effects of administration of the test substance on weight measurements and necropsies were not recognized. Based on the results of intramuscular administration of a single dose of hzVSF-v13 to rats under the conditions of this test, the approximate lethal dose has been determined to exceed 80 mg/kg in both male and female animals.

- Repeat-dose toxicity test

• The results of 4-week repeat-dose and 4-week recovery tests in rats were as follows. This test was performed to evaluate the toxic responses and safety observed in necropsies performed 2 weeks after the final administration of the repeated intravenous administration of hzVSF-v13 to male and female Sprague-Dawley (Crl: CD [SD]) rats 3 times weekly for 2 weeks—6 times in total—and to set a 4-week recovery group and evaluate the reversibility of toxic changes. The test substance was administered intravenously at 3 doses—6.25, 25 and 100 mg/kg—to 10, 10 and 15 each of male and female animals in each group 6 times in total for 2 weeks. A control group (DPBS) was set as well, and intravenous administration was given to 15 animals 6 times in total for 2 weeks. A 4-week recovery period was scheduled from 2 weeks after the final administration in order to evaluate the reversibility of toxicity in 5 each of male and female animals in the control group and 100 mg/kg treatment group.

In addition, a toxicokinetic test group was set, and 3 each of male and female animals in each group were analyzed at each time point of blood collection. General symptom observation, body weight measurement, feed intake measurement, functional test (only applicable to the main test group), ophthalmologic examination, and urinalysis were performed during the observation period, and hematology, blood biochemistry, organ weight measurement, visual inspection at necropsy, and histopathological examination were performed after the end of the observation period. The systemic exposure level of the drug was confirmed as well through a toxicokinetic test. No effect of administration of the test substance on the general symptoms, weight, feed intake, ophthalmologic examination, urinalysis, hematology, blood biochemistry, organ weight, and necropsy was observed in male and female animals in the 6.25, 25 and 100 mg/kg treatment groups. As a result of the histopathological examination, no effect of administration of the test substance was observed in male and female animals in the 100 mg/kg treatment group. In addition, it was determined that there was local tolerance because evidence of myofiber damage was not observed at the administration site of male and female animals in the 6.25, 25 and 100 mg/kg treatment groups. During the 2-week administration period, an increase in the blood concentration was observed as the number of doses administered increased at all doses. The highest concentration was observed after the administration (0.5 hr) at the final administration day (Day 14) (excluding male low-dose group), and a decrease in the blood concentration was observed during the following 6-week observation period. The systemic exposure level (AUC_{all}, C_{max}) increased at a ratio similar to the increase in administration dose, and it is determined that there was no difference between the gender. As described above, based on the results of repeated intravenous administration of the test substance hzVSF-v13 to rats 3 times weekly for 2 weeks—6 times in total—under the conditions of this test, the no-observed-adverse-effect level (NOAEL) has been determined to be not less than 100 mg/kg in both male and female animals.

- The results of 4-week repeat-dose and 4-week recovery tests in beagle dogs were as follows. This test was performed to evaluate the toxic responses and safety observed in necropsies performed 2 weeks after the final administration of the repeated intravenous administration of the test substance hzVSF-v13 at doses of 0 (control group), 6.25, 25 and 100 mg/kg 3 times weekly for 2 weeks using 3 each of male and female beagle dogs per group. Furthermore, starting from 2 weeks after the final administration, a 4-week recovery group composed of 2 each of male and female animals was set in the control group and the high-dose group to check the reversibility of the toxic changes. Also, a toxicokinetic test was performed to evaluate the systemic exposure level of the drug. Animal deaths did not occur in male and female animals in all test groups during the test period. However, symptoms deemed to be hypersensitivity reactions, such as hypoactivity, vomiting, paleness, or hyperemia, were observed after the 4th to 6th administrations in male and female animals in the 100 mg/kg treatment groups, and after the 6th administration in the 25 mg/kg treatment group. In the histopathological examination, the size of germinal centers of the spleen increased in male and female animals in all test substance treatment groups, and this is considered to be due to the immune response of the test substance. No toxicological effect of administration of the test substance on the weight, feed intake, eye examination, electrocardiography, urinalysis, hematology, blood biochemistry, organ weight, necropsy and local tolerance test was observed. In the toxicokinetic test, the systemic exposure level (AUC_{all}, C_{max}) of the test substance hzVSF-v13 increased in proportion to the increase in administration dose, and it increased according to the increase in the number of doses administered. The highest blood concentration (T_{max}) was observed at Day 11 (5th administration) in several treatment groups, and after the administration (at 0.5 hr) at Day 14 (6th administration) in several treatment group. Thereafter, the blood concentration gradually decreased from Week 3, and no difference was observed between male and female animals. In addition, as a result of measuring anti-drug antibodies (ADAs) against hzVSF-v13, it was confirmed that ADAs were produced in most of the animals starting from about 11 days after initiating administration of the test substance. Due to the results described above, it has been determined that the no-observed-adverse-effect level (NOAEL) for male and female beagle dogs under these test conditions is 6.25 mg/kg.

6. OBJECTIVES OF THE CLINICAL STUDY

6.1. PRIMARY OBJECTIVE

To evaluate the safety and tolerability after intravenous administration of a single dose of the study drug hzVSF-v13 in healthy male subjects.

6.2. SECONDARY OBJECTIVE

To evaluate the pharmacokinetic characteristics after intravenous administration of a single dose of the study drug hzVSF-v13 in healthy male subjects.

7. INVESTIGATIONAL PRODUCT

7.1. STUDY DRUG

Generic Name (Code Name)	Active Ingredient	Amount	Other Additives	Storage Method	Remarks
hzVSF-v13	hzVSF	40 mg/ml x 5 ml	L-histidine Histidine hydrochloride polysorbates 20 Sucrose Water for injection	2 to 8℃, Sealed container	

7.2. PLACEBO

Normal saline

7.3. EXPECTED ADVERSE EVENTS (SIDE EFFECTS) AND PRECAUTIONS FOR USE

7.3.1. EXPECTED SIDE EFFECTS FROM NON-CLINICAL LABORATORY STUDIES RESULTS

Since hzVSF-v13 has never been administered to human subjects, there are no known adverse events. Also, since there are no similar drugs of the same class targeting vimentin or mutant vimentin, it is not possible to predict adverse events based on the adverse event reports of similar drugs. During the observation period in the 4-week repeat-intravenous-dose toxicity test in beagle dogs, no animal deaths occurred in male and female animals in all test groups, and no symptoms were observed until the 3rd administration. However, after the 4th and 5th administration (9 and 11 days after initiating the administration), symptoms such as hypoactivity, vomiting, paleness, or hyperemia were observed in 2 to 3 out of 5 male animals and 4 out of 5 female animals in the 100 mg/kg treatment group. At the 6th administration (14 days after initiating the administration), symptoms such as hypoactivity, vomiting, paleness, or hyperemia were observed in all female and male animals in the 25 mg/kg treatment group, and 4 out of 5 male animals and 3 out of 5 female animals in the 100 mg/kg treatment group. Besides, 1 to 2 cases of soft stool were observed in the control group and 1 each of female animals the 6.25 and 25 mg/kg treatment groups, and no symptoms were observed in the recovery group.
During the observation period in the 4-week repeat-intravenous-dose toxicity test using rats, cases of death and abnormal general symptoms were not observed in male and female animals in the 6.25, 25 and 100 mg/kg treatment groups during the administration period. Loss of teeth was observed in 1 female animal in the control

group, but it was an incidental change observed in the control group. During the recovery period, cases of death and abnormal general symptoms were not observed in male and female animals in the control group and the 100 mg/kg treatment group.

7.4. PACKAGING AND LABELING

The packaging container of the investigational product shall be labeled in Korean containing the following information:

- "For Clinical Trial Use Only" indication
- Name or drug identification mark of the investigational product
- Batch number or code number
- Name, address and telephone number of the sponsor (IND holder in the case that a clinical study plan has been approved)
- Shelf life
- Storage condition
- Reference code that identifies the clinical study
- Subject identification number, clinical drug number, and visit number (These can be documented and omitted if documentation is unnecessary.)

7.5. STORAGE

A clinical trial pharmacist who manages the investigational products (hereinafter, "clinical trial pharmacist") is responsible for the receipt, storage, dispensation, management and return of the investigational products used in the clinical study. The clinical trial pharmacist should confirm the receipt of the investigational products and the number of products in writing, sign and manage them properly. The clinical trial pharmacist should ensure that the investigational products are administered to the subjects only in accordance with the protocol, and the records of the management of all investigational products provided to each subject should be accurate. Unused investigational products will be stored at 2 to 8℃ until the sponsor makes a decision on destruction or recall. Upon the end of study, all unused drugs and a copy of the investigational product management record have to be sent to the clinical research associate in charge of this study.

8. TARGET DISEASES

Influenza, hepatitis B and C

9. Subjects

9.1. NUMBER OF SUBJECTS

The targeted number of subjects is 56 subjects in total, and 4 or 8 subjects will be assigned per dose group.

hzVSF-v13 IV 10 mg, 20 mg – 4 subjects in each dose group
(3 subjects for the study drug, 1 subject for the placebo)

hzVSF-v13 IV 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, 1,200 mg – 8 subjects in each dose group

(6 subjects for the study drug, 2 subject for the placebo)

- Single-dose study (intravenous administration)

Dose Group	Number of Subjects
Group 1 (10 mg IV)	hzVSF-v13: 3 subjects Placebo: 1 subject
Group 2 (20 mg IV)	hzVSF-v13: 3 subjects Placebo: 1 subject
Group 3 (50 mg IV)	hzVSF-v13: 6 subjects Placebo: 2 subjects
Group 4 (100 mg IV)	hzVSF-v13: 6 subjects Placebo: 2 subjects
Group 5 (200 mg IV)	hzVSF-v13: 6 subjects Placebo: 2 subjects
Group 6 (400 mg IV)	hzVSF-v13: 6 subjects Placebo: 2 subjects
Group 7 (800 mg IV)	hzVSF-v13: 6 subjects Placebo: 2 subjects
Group 8 (1200 mg IV)	hzVSF-v13: 6 subjects Placebo: 2 subjects

9.2. RATIONALE FOR CALCULATION OF THE NUMBER OF SUBJECTS

The purpose of the study is exploratory which is not to verify statistical hypotheses, and in the case of Phase 1 clinical studies being conducted using new drugs for which safety is not established, it is ethically desirable to conduct the study in the minimum number of subjects while satisfying the study objectives. In addition, dose groups had a certain ratio of subjects who will receive the placebo to enable double-blind for an objective safety and tolerability review. In this study, for the low dose groups (Groups 1 and 2), the sentinel dose groups, the target number of subjects per dose group has been set to 4 subjects per dose group, and the target number of subjects for other dose groups has been set to 8 subjects per dose group.

9.3. SUBJECT INCLUSION/EXCLUSION CRITERIA

9.3.1. Inclusion Criteria

1) Healthy males aged 19 to 45 years inclusive at the time of the screening visit
2) Individuals with a BMI of not less than 18.0 kg/m^2 to not more than 27.0 kg/m^2 and weighed not less than 55 kg and less than 90 kg at the time of the screening visit
3) Individuals confirmed clinically healthy based on medical history, physical examination, vital sign, electrocardiography (ECG), and appropriate clinical laboratory tests (provided that individuals outside the normal range may participate subject to investigator discretion)
4) Individuals who have agreed to use a medically acceptable method of dual contraception and not to

donate sperm from the first day until 30 days after the last day of investigational product administration

5) Individuals who have voluntarily decided to participate in this clinical study and have given a written consent to comply with the requirements of the clinical study

9.3.2. Exclusion Criteria

1) Individuals with a clinically significant hepatic, renal, digestive, respiratory, musculoskeletal, endocrine, neuropsychological, hemato-oncologic, cardiovascular, or other disease or history
2) Individuals with a clinically significant history of hypersensitivity reactions to the components of hzVSF-v13, drugs containing components of the same class, or other drugs (aspirin, non-steroidal anti-inflammatory drugs, antibiotics, etc.)
3) Individuals with a positive result in the immunogenicity test for hzVSF-v13 conducted during the screening test
4) Individuals who have a history of drug abuse, or who have positive in the test for abuse-likely drugs in the urine drug screening test
5) Individuals with abnormal results for any of the following vital signs at the time of the screening visit:
   A. Systolic blood pressure: < 90 mmHg or > 140 mmHg
   B. Diastolic blood pressure: < 50 mmHg or > 90 mmHg
   C. Heart rate: < 50 bpm or > 90 bpm
6) Individuals with abnormal results for any of the following ECG items at the time of the screening visit:
   A. PR > 210 msec
   B. QRS complex: > 120 msec
   C. QTc > 450 msec
7) Individuals who have participated in another clinical study or bioequivalence study and received an investigational product within 3 months prior to the first day of administration (provided that 6 months from 06/12/2019)
8) Individuals who have donated whole blood within 2 months prior to the first day of administration, or donated blood components or received blood within 1 month prior to the first day of administration
9) Individuals who have taken drug-metabolizing enzyme inducers or inhibitors, such as barbitals, within 1 month prior to the screening
10) Individuals who have consumed grapefruit/caffeine-containing foods within 3 days of the first administration, and individuals who are unable to avoid consuming grapefruit-containing foods from 3 days prior to admission until the date of discharge
11) Individuals who have taken prescription drugs or oriental medications within 2 weeks prior to the first day of administration, or who have taken over-the-counter (OTC) drugs within 1 week prior to the first day of administration (provided that individuals who meet other requirements may participate in the clinical study subject to investigator discretion)
12) Individuals who consume high amounts of caffeine or alcohol and individuals who are heavy smokers (caffeine > 5 units/day, alcohol > 21 units/week (1 unit = 10 mL of pure alcohol), smoking > 10 cigarettes/day)
13) Individuals who are unable to eat meals provided by the study site
14) Individuals who have participated in this study
15) Individuals who have a positive result for serology (hepatitis B, human immunodeficiency virus [HIV], and hepatitis C tests)
16) Individuals with veins that are not suitable for intravenous catheter insertion or multiple venipunctures
17) Individuals who do not agree to use a medically acceptable method of dual contraception from the first day until 30 days after the last day of investigational product administration
18) Other individuals deemed unsuitable as a subject by an investigator

9.4. SUBJECT NUMBER

4-figure screening numbers starting from S001 will be assigned to the volunteers who provided a written consent to participate in the clinical study in the order of the informed consent form signed (e.g., S001, S002, etc. will be assigned in the order of the informed consent form signed).

Subject ID will be assigned in the order of passing the screening tests finally. If the subjects pass the screening tests on the same day, subject numbers will be assigned in the order of the informed consent form signed. The subject ID is composed of five figures starting from R1001—the first figure indicates whether a subject has been substituted (1: not a substituted subject; 2: a substituted subject), the second figure indicates the dose group, and the last two digits indicate the order of the subjects participating in this study.

The subject ID assigned to each subject will be used as subject identification codes that identify the subjects until the end of the clinical study.

- Single-dose study (intravenous administration)

Dose Group	Subject Number
Group 1 (10 mg IV)	R1101 ~
Group 2 (20 mg IV)	R1201 ~
Group 3 (50 mg IV)	R1301 ~
Group 4 (100 mg IV)	R1401 ~
Group 5 (200 mg IV)	R1501 ~
Group 6 (400 mg IV)	R1601 ~
Group 7 (800 mg IV)	R1701 ~
Group 8 (1200 mg IV)	R1801 ~

9.5. SUBJECT PRECAUTIONS/RESTRICTIONS

In principle, no food intake should be allowed except for the foods and drinking water provided during the hospitalization period; however, snacks will be allowed to be provided as long as they do not have any impact on the clinical study. Ingestion of caffeinated or grapefruit-containing beverages or foods, cigarette

smoking and alcohol consumption will be prohibited from 3 days before the admission until the day of discharge. Also, strenuous exercises exceeding activities of daily living will be prohibited and use of contraception has to be maintained throughout the clinical study period. In addition, the subjects will be required to fast, except for drinking water, after 10 p.m. on the day before the scheduled date of clinical laboratory tests, and any external factors that could have an effect on the clinical laboratory tests (drinking, smoking, strenuous exercise, etc.) will be restricted if possible prior to the tests even after the discharge. In addition, fluid intake is also prohibited from an hour before the administration to 2 hours after the administration, and food intake is prohibited for 4 hours after the administration.

9.6. DROP-OUT AND SUBJECT SUBSTITUTION

"Enrollment" refers to the randomization (assignment of subject ID) of subjects participating in the study (i.e., those who signed the informed consent form) due to their eligibility based on the inclusion/exclusion criteria. Incompletion of a study by an enrolled subject is called "drop-out." The drop-out of a subject may be decided at any time during the study period. A subject who applies to one of the situations shown below is processed as a dropout, and the date of drop-out, date of the last administration and reason for drop-out have to be recorded in a CRF at the moment of drop-out.

1) In the case that a subject requests discontinuation of the investigational product administration during the clinical study, or withdraws his consent to participation in the study

2) In the case that a subject has received a drug that is expected to affect the evaluation of the safety or pharmacokinetics of the study drug during the clinical study

3) In the case that serious adverse events/adverse drug reactions have occurred

4) In the case that a subject is unable to perform blood sampling for the testing for pharmacokinetics/safety

5) In the case that significant protocol violation cases are newly identified during the clinical study

6) In the case that the sponsor or the Ministry of Food and Drug Safety requests discontinuation

7) In the case that the principal investigator/investigator determines that the study has to be discontinued due to other reasons

This study allows enrollment of a small number of backup subjects in advance considering the drop-out rate prior to the initial administration, and a dropped out subject may be substituted with a backup subject in case of dropping out prior to the initial administration. In the event of more than 2 subjects in the same dose group drop out after administration of the investigational product, substitution of the subjects shall be decided after a discussion among the principal investigator, sponsor, pharmacokinetic and statistical analysts. The first figure of the substituted subject's subject number will be 2, and the last 3 figures will be the same number as the dropped out subject's subject number (e.g., if Subject R1104 drops out and is replaced, the subject number to be assigned will be R2104). The substituted subject will be assigned to the same dose group as the dropped out subject. The test results of the relevant subject may be reviewed in the finally evaluable items up until the time of discontinuation/drop-out.

9.7. STUDY COMPLETION

"Completion" in this clinical study refers to the case that the subject meets the inclusion/exclusion criteria specified in the protocol and has completed the entire study process and all visits.

9.8. BACKUP SUBJECTS (SUBJECT CANDIDATES)

This study can recruit backup subjects (subject candidates) for smooth progress. Those who participate as backup subjects and have not received the study drug will be sent home after other subjects complete the initial administration, and backup subjects may participate in the next treatment group.

10. ANALYTICAL METHOD

10.1. STUDY DESIGN

This is a Phase 1, dose blocked-randomized, double-blind, placebo controlled, single dosing, dose-escalation study to investigate the safety, tolerability, pharmacokinetic characteristics of hzVSF-v13 after intravenous administration in healthy male subjects. Subjects will be randomized to the test group and the control group at a 3:1 ratio in each dose groups; however, in the case of all dose groups except for Group 1 and Group 2 (Group 3–Group 8), the first 3 out of 8 subjects in each dose group will be randomized to be 2 subjects for the study drug and 1 subject for the placebo. Collection of adverse events, physical examinations, vital sign, electrocardiography (12-lead ECG), clinical laboratory tests, immunogenicity test, etc. will be performed to evaluate the safety and tolerability, and blood collection will be carried out to evaluate the pharmacokinetic characteristics.

RATIONALE FOR ADMINISTRATION DOSES

· Human Equivalent Doses and MRSD

Species	NOAEL	HED by FDA guidance	Safety factor (1/10)	Human (60kg) dose
Rat	100 mg/kg	100 mg/kg	10 mg/kg	600 mg
Dog	6.25 mg/kg	6.25 mg/kg	0.625 mg/kg	37.5 mg

In the homogeneous population of health volunteers with similar demographic characteristics, the effect of differences in individual weights on pharmacokinetic characteristics is considered to be insignificant. In addition, if the drug is administered at doses depending on body weights or body surface areas, there may be difficulties to conduct the study compared to administration at a fixed dose, and there may be difficulties compared to administration at a fixed dose even in evaluation of the safety and tolerability. Therefore, the administration dose of the investigational product will be a fixed dose.

The results of beagle dogs, which are the most sensitive species of those applied, have confirmed that the maximum no-observed-adverse-effect level (NOAEL) is 6.25 mg/kg. Large molecules (not less than 100,000 daltons), such as antibodies, are scaled by body weight, not by body surface area [HED (mg/kg) = NOAEL (mg/kg)]. In this case, the human equivalent dose (HED) converted into weight of the maximum no-observed-adverse-effect level (NOAEL) is 6.25 mg/kg, and the maximum recommended starting dose (MRSD), given a safety factor of 10, is 37.5 mg, assuming that healthy adult males weigh 60 kg.

Furthermore, pharmacological effects that suppress viral replication and inflammatory reaction have been

confirmed at 2 mg/kg upon intravenous administration to influenza mouse models. The human equivalent dose (HED) of this dose converted into weight that has been scaled by body weight [HED (mg/kg) = NOAEL (mg/kg)] is 2 mg/kg, and given a safety factor of 10, it is 12 mg respectively, assuming that healthy adult males weigh 60 kg.

Therefore, the initial administration dose has been determined to be 10 mg taking into account that the weight-corrected pharmacologically active dose is the smaller dose between the MRSD and the weight-corrected pharmacologically active dose.

RATIONALE FOR BLOOD COLLECTION TIMES

The pharmacokinetic parameters reported in animal studies on intravenous administration of hzVSF-v13 are as shown below.

LC51-0255	BW (kg)	CL (mL/day/kg)	Vd_{7d} (mL/kg)
Mouse	0.03	2.80 – 4.90	54.03 – 62.80
Rats	0.3	1.21 – 1.70	42.30 – 56.79
Dogs	10.0	1.58 – 2.19	46.87 – 51.99

Considering that the half-life of the study drug in the human body estimated using the allometry method based on these is estimated to be approximately 23 to 34 days, the half-life of the study drug is estimated to be approximately 30 days. Therefore, the last blood collection time point has been set as 2,184 hours (92 d 0 h). Based on these, the pharmacokinetic blood collection time points in the single-dose study have been set as follows: 0 h (pre-dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 336 (15 d 0 h), 504 (22 d 0 h), 672 (29 d 0 h), 840 (36 d 0 h), 1,176 (50 d 0 h), 1,512 (64 d 0 h), 1,848 (78 d 0 h) and 2,184 h (92 d 0 h; post-dose) (26 points).

Excluding the volunteers who were positive in the immunogenicity test for hzVSF-v13 during the screening tests, the blood collection time points in the single-dose study have been set as the time of screening tests, 168 (8 d 0 h), 336 (15 d 0 h), 672 (29 d 0 h), 1,344 (57 d 0 h), 2,184 h (92 d 0 h; post-dose) (6 points) in order to confirm the production of antibodies against hzVSF-v13.

DEFINITION OF DOSE-LIMITING TOXICITY (DLT)

Dose limiting toxicity (DLT) is hematologic or non-hematologic toxicity related to the investigational product, and it is defined as adverse events of at least Grade 3 based on the National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

DOSE ESCALATION/DISCONTINUATION CRITERIA

Each dose group will have hzVSF-v13 and the placebo randomized at a 3:1 ratio to conduct the clinical study. The study will be proceeded sequentially from the lowest dose, and whether to proceed with the next dose will

be determined based on the tolerability and safety results of the previous dose.

Each subject in Group 1 and Group 2 will be administered, and if no significant dose-limiting toxicity (DLT) occurs within 72 hours, then the next subject will be administered.

In the case of all dose groups except for Group 1 and Group 2 (Group 3–Group 8), 3 out of 8 subjects in each dose group (2 subjects for the study drug and 1 subject for the placebo) will receive the investigational product (hzVSF-v13 or placebo) at least 72 hours earlier than the remaining subjects in the same dose group. If no significant dose-limiting toxicity occurs within 72 hours, the remaining subjects in the relevant dose group will receive the investigational product (hzVSF-v13 or placebo) depending on the randomization.

In the case that at least 3 subjects experience a Grade 3 adverse event or at least 1 subject in certain dose groups experience a Grade 4 adverse event based on the CTCAE published by the United States NCI, the principal investigator shall consult the independent SMC, established separately from this study, and discuss discontinuation of the relevant dose group and dose escalation with the sponsor. (For Group 1 and Group 2, discontinuation of the dose group and dose escalation shall be considered based on the following criterion: occurrence of Grade 3 adverse event in at least 2 subjects or Grade 4 adverse event in at least 1 subject.)

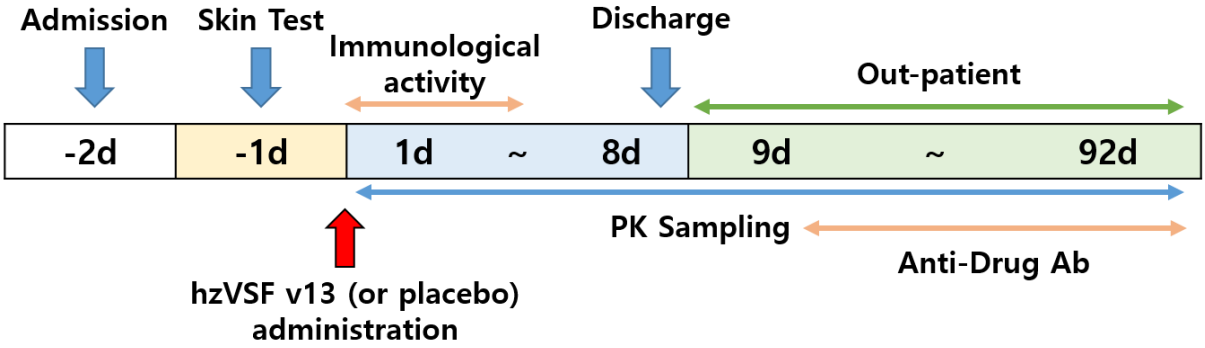
Empirically, acute stage adverse events, such as acute hypersensitivity reactions requiring therapeutic interventions, are considered assessable by observing for 2 weeks after administration of the investigational product. Accordingly, after all subjects complete all scheduled tests up to 15 d for each dose group, the SMC will evaluate the safety-related data. With reference to the evaluation result of the SMC, the principal investigator and the sponsor will decide by mutual consent whether to continue the clinical study and to proceed with the next step.

OVERALL SCHEDULE

The screening tests shall only be performed in volunteers within 4 weeks prior to the first day (1 d) of investigational product administration (−28 d to −2 d) in order to select the subjects considered to be eligible for this clinical study. The selected subjects will be randomly assigned to either the test group or the control group (−1 d) and will be admitted to the Seoul National University Hospital Clinical Trials Center 2 days (-2d) prior to administration of the investigational product.

- **Single-Dose Study (Intravenous Administration)**

- 10 mg, 20 mg, 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, 1,200 mg IV



The selected subjects will be admitted to the Seoul National University Hospital Clinical Trials Center 2 days (-2d) prior to administration of the investigational product. The skin test will be performed a day (-1 d) prior to administration of the investigational product. Only the subjects who did not have clinically significant findings in the skin test will have intravenous (IV) administration of the investigational product (hzVSF-v13 or placebo) at 9 a.m. on the day (1d) of investigational product administration. The subjects will be required to perform the clinical study procedures in accordance with the predefined schedule and will be discharged 7 days (8d) after the administration. Thereafter, the subjects will visit the Seoul National University Hospital Clinical Trial Center as outpatients from 9 d to 92 d in order to perform the clinical study procedures according to the predefined schedule. After completing all scheduled tests up to 15 d for each dose group, an independent SMC, established separately from this study, will evaluate the safety-related data. With reference to the evaluation result of the SMC, the principal investigator and the sponsor will decide by mutual consent whether to continue the clinical study and to proceed with the next step.

10.2. RANDOMIZATION, MAINTAINING DOUBLE-BLIND AND UNBLINDING

RANDOMIZATION

For randomization in this clinical study, an independent person in charge of randomization will randomize using SAS® ver. 9.3 (or a later version) and provide a randomization table for a code manager. The person in charge of randomization will deliver randomization codes, which will be prepared before the study, to the code manager, and the investigator will assign subject numbers in the order of subjects' enrollment in the study. Each subject will be assigned the investigational product (study drug or placebo) according to the relevant subject number, and the clinical trial pharmacist will dispense the investigational product (study drug or placebo) assigned for each subject number. Randomization codes will be kept separately by the administrator. Using random numbers that are only open to the code manager as seed numbers, subjects could be assigned to the study group and the control group at a 3:1 ratio in each dose group. However, in the case of all dose groups except for Group 1 and Group 2 (Group 3–Group 8), the first 3 out of 8 subjects in each dose group shall be randomized to be 2 subjects for the study drug and 1 subject for the placebo.

DOUBLE-BLIND

As it has been designed to investigate the safety, tolerability and pharmacokinetic characteristics after intravenous administration of a single dose of hzVSF-v13, it will be conducted using a double-blind method for each dose group.

MAINTAINING DOUBLE-BLIND

1. Confirmation that the investigational product cannot be distinguished

The clinical trial pharmacist will dispense the study drug or placebo in a normal saline bag prepared to maintain double blinding, thereby maintaining double blinding for the principal investigator and the subjects. The label indicated in the protocol is a label for the study drug and placebo that are only provided to the pharmacy, and neither the principal investigator nor the subject will be aware of the type of drug being administered prior to the end of the study. The investigational products will be monitored by a separate clinical research associate who is not involved in this clinical study, and the relevant clinical research associate and the clinical trial pharmacist will be exempted from blinding.

2. Preparation and maintenance of the randomization code and blinding envelop

The code manager will generate randomization codes according to the randomization method, and the clinical trial pharmacist will dispense the investigational product (study drug or placebo) assigned for each subject number accordingly. The randomization codes shall be kept safe until unblinding occurs.

The investigational product assigned to each subject will be decided based on the relevant randomization number, and the randomization codes shall not be disclosed unless the randomization codes are unblinded upon termination of the clinical study for each stage. However, to be prepared for unblinding due to occurrence of an emergency situation, such as a serious adverse event, the code manager will make a blinding envelop with randomization numbers and deliver it to the investigator for storage. In addition, the blinding envelop should be stored properly by the sponsor and the principal investigator until the end of the clinical study and can only be opened by a prescribed procedure.

3. Storage of the investigational product

The blinding status should be maintained before unblinding. For this, the remaining investigational products have to be stored and sealed properly.

UNBLINDING

1. Unblinding process at the end of each study or the clinical study

After the end of each study or the the clinical study and all case report forms and data (excluding blood concentration measurement results) are locked, the final unblinding (randomization code for each stage) should be done.

After the data are locked, the investigator makes a request for unblinding (e-mail, fax, etc.) to the code manager. The code manager records all information related to unblinding (unblinding date, time, and name of investigator

requesting unblinding) and send unblinded randomization codes for each stage to the investigator (e-mail, fax, etc.).

2. Unblinding process at an emergency situation

The unblinding process for unblinding due to occurrence of an emergency situation, such as a serious adverse event, is as follows:

1) The subject's safety results will be evaluated based on the United States NCI "CTCAE version 4.03." For reference, in the case of being determined as a clinically significant finding, the investigator should evaluate the causal relationship to the investigational product while blinded.

2) Before unblinding individually, the investigator will send the relevant information to the sponsor.

3) It should be confirmed whether at least half of the members required to be present when unblinding have participated (participants when unblinding: principal investigator, investigators, and sponsor's representative).

4) All attendees will share and reconfirm the reason for unblinding.

5) Randomization codes will be unblinded and disclosed by opening the blinding envelop, etc.

6) After all participants confirm the disclosed randomization codes, they will sign for confirmation on a randomization code disclosure confirmation form.

7) In the case that adverse events occur in the hzVSF-v13 treatment group, the investigator and the sponsor must discuss whether to continue the clinical study. In the case that adverse events occur in the placebo group, the clinical study shall continue without having a discussion.

8) in the case that immediate disclosure of randomization codes is required to ensure the rights and interests as well as safety of the subject, the subject's code may be disclosed under the responsibility of the person in charge of disclosure. At this time, the person in charge of disclosure shall immediately inform the sponsor of the randomization information of the subject and the disclosure.

10.3. METHOD OF INVESTIGATIONAL PRODUCT ADMINISTRATION

◆ **Single-Dose Study (Intravenous Administration)**

The relevant dose of hzVSF-v13 (10–1,200 mg) will be dissolved in 100 mL of 0.9% normal saline solution and administered intravenously for approximately 30 minutes at 9 a.m. of 1 d.

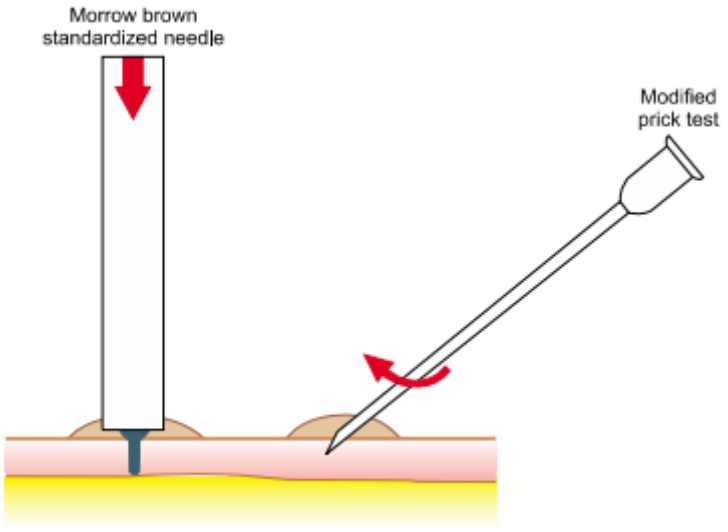
10.3.1. Other Combination Therapies

In principle, no other drugs should be administered during the clinical study, except for the investigational products stated in the protocol. However, drugs may be administered depending on the decision of the principal investigator, if they are necessary to treat adverse events, etc. If a drug taken arbitrarily by a subject

without the decision of the principal investigator is expected to possibly have an effect on the safety and pharmacokinetic evaluation in this clinical study, the subject will drop out (see 9.6 Drop-out and Subject Substitution). The drug name (product name), administration route, daily dose, dosing period, reason for administration, etc. of all drugs (prescription drugs and over-the-counter drugs) administered concomitantly during the clinical study period have to be recorded in a CRF.

10.4. SKIN TEST METHOD

- To be performed by an expert who is easily able to perform the procedure and interpret the result.
- Perform in the environment where can handle dangerous situations such as anaphylaxis.
- Site to be performed: Perform on the inside the forearm
- Wipe the area to be performed with an alcohol swab and dry it, and then drop hzVSF-v13, positive control solution (histamine, 1 mg/mL), and negative control solution (normal saline) on the skin at a distance of at least 2 to 3 cm.
- Lift the skin slightly with a lancet or needle to allow the test solutions to reach the epidermis.
- Concentration of procedure: Perform the test at a concentration diluted to approximately 1/10 of the scheduled dose of hzVSF-v13, and then increase to a concentration of 1/1.
- If the result is negative at 15 to 20 minutes after performing at a concentration of 1/10, proceed to a 1/1 concentration.
- Positive response: In the case that a wheal of at least 3 mm or swelling of at least the same size as the positive control solution accompanies redness



(Adkinson et al. Middletone's Allergy, Principle & practice 7th edition)

10.5. DETAILS OF THE CLINICAL STUDY SCHEDULE

10.5.1. Screening Tests

The screening tests to review the eligibility of the subjects who voluntarily provided a written consent to participate in the clinical study will be performed within 4 weeks from the initial administration (−28 d to −1 d), and any subjects who have clinically significant abnormalities in the following tests shall be excluded:

- Demographic information and history taking
- Vital signs
- Physical examination
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- 12-lead ECG (electrocardiography)
- Immunogenicity Test
- Checking on the concomitant medications
- Urine drug screening
  Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates
- Serology
  HBsAg, anti-HCV Ab, anti-HIV (Ag, Ab) tests

10.5.2. Single-Dose Study (Group 1 to Group 8)

◆ **Admission (−2 d to 8 d)**

All subjects will be admitted to the Clinical Trials Center 2 days prior to the administration (−2 d). During this time, all subjects will perform the following procedures:

- Skin test
  -1d
- Randomization/subject numbers assigned (to be done after the skin test at −1 d)
- Administration of the investigational product

  The subjects will be administered the investigational product (hzVSF-v13 or the placebo) on an empty stomach at 9 a.m. at 1 d. The subjects shall fast, except for drinking water, from 10 p.m. at −1 d. Water intake shall be prohibited from an hour before the administration to 2 hours after the administration.
- Vital signs
  1d 0h(pre-dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 24(2d 0h), 36(2d 12h), 48(3d 0h), 60(3d 12h), 72(4d 0h), 96(5d 0h), 120(6d 0h), 144(7d 0h), 168h(8d 0h)(post-dose)(systolic blood pressure, diastolic blood pressure, pulse rate, and temperature)
- Physical examination
  1d 0h(pre-dose), 168h(8d 0h)(post-dose)
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)
  1d 0h(pre-dose), 24(2d 0h), 72(4d 0h), 168h(8d 0h)(post-dose)
- 12-lead ECG (electrocardiography)
  1d 0h(pre-dose), 168h(8d 0h)(post-dose)
- Blood collection for pharmacokinetics
  1d 0h(pre-dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 24(2d 0h), 36(2d 12h), 48(3d 0h), 60(3d

12h), 72(4d 0h), 96(5d 0h), 120(6d 0h), 144(7d 0h), 168h(8d 0h) (post-dose)

- Immunogenicity Test

  1d 168h(8d 0h)(post-dose)
- Monitoring of adverse events
- Checking on the concomitant medications

The subjects who completed the clinical study procedures according to the predefined schedule will be allowed to be discharged in the morning at 8 d.

◆ **Outpatient (9 d to 92 d)**

All subjects will visit the Seoul National University Hospital Clinical Trial Center as outpatients after discharge in order to perform the clinical study procedures according to the predefined schedule. During this time, all subjects will perform the following procedures:

- Vital signs

  1d 336(15d 0h), 504(22d 0h), 672(29d 0h), 840(36d 0h), 1176(50d 0h), 1512(64d 0h), 1848(78d 0h), 2184h(92d 0h)(post-dose)(systolic blood pressure, diastolic blood pressure, pulse rate, and temperature)
- Physical examination

  1d 336(15d 0h), 504(22d oh), 672(29d 0h), 840(36d 0h), 1176(50d 0h), 1512(64d 0h), 1848(78d 0h), 2184h(92d 0h)(post-dose)
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)

  1d 336(15d 0h), 504(22d oh), 672(29d 0h), 840(36d 0h), 1176(50d 0h), 1512(64d 0h), 1848(78d 0h), 2184h(92d 0h)(post-dose)
- 12-lead ECG (electrocardiography)

  1d 336(15d 0h), 504(22d oh), 672(29d 0h), 840(36d 0h), 1176(50d 0h), 1512(64d 0h), 1848(78d 0h), 2184h(92d 0h)(post-dose)
- Blood collection for pharmacokinetics

  1d 336(15d 0h), 504(22d oh), 672(29d 0h), 840(36d 0h), 1176(50d 0h), 1512(64d 0h), 1848(78d 0h), 2184h(92d 0h)(post-dose)
- Immunogenicity Test

  1d 336(15d 0h), 672(29d 0h), 1344(57d 0h), 2184h(92d 0h)(post-dose)
- Monitoring of adverse events
- Checking on the concomitant medications
- Tolerability/safety assessments

  The tolerance and safety of the relevant dose group shall be evaluated after completing all scheduled tests up to 15 d in order to determine whether to proceed to the next dose group.

If the investigator decides that additional visits are necessary for the safety of the subjects, the subjects may need to visit the Seoul National University Hospital Clinical Trials Center additionally.

10.5.3. Early Termination Visit

If a subject drops out prior to the administration, no separate safety assessments will be performed. If a subject drops out during the hospitalization, the scheduled dose will be discontinued, and the subject will be discharged after completing the vital sign~~,~~ electrocardiography, clinical laboratory tests, physical examination, and monitoring of adverse events and checking on concomitant medications by the next morning if possible. In case of dropping out, the dropped out subject will be requested to visit the Clinical Trials Center within 4 weeks (28 days) from the date of drop-out if possible in order to perform the following observation and tests:

- Physical examination
- Vital signs
- Electrocardiography (12-lead ECG)
- Clinical laboratory tests
- Monitoring of adverse events
- Checking on the concomitant medications

If a subject drops out prior to the administration, no separate safety assessments will be performed. If the investigator decides that additional visits are necessary for the safety of the subjects, the subjects may need to visit the Seoul National University Hospital Clinical Trials Center additionally.

10.5.4. Discontinuation of the Clinical Study

In the case that the principal investigator determines that continuation of the clinical study is not a wise decision based on the results observed during the process of the clinical study, the principal investigator may discontinue a part of the study or the whole study after having a discussion with the sponsor.

- If the principal investigator determines that a subject cannot continue the clinical study due to a serious reason that has occurred during the clinical study and emergency measures are required, the principal investigator may discontinue a part of the clinical study or the whole clinical study even without a discussion with the sponsor.
- The sponsor may discontinue a part of the clinical study or the whole clinical study for a reason of safety or management.
- In case of early termination or temporary suspension of the clinical study, the principal investigator has to notify the subjects, take action and follow up adequately.
- CRFs, clinical study progress reports and clinical study results up to the moment of discontinuation have to be summarized and delivered to the sponsor, and all data related to the study (complete or incomplete CRFs, CRFs without entries, investigational products, etc.) have to be returned to the sponsor.
- In the event of discontinuation of the clinical study, it has to be reported to the Institutional Review Board (IRB) and the Ministry of Food and Drug Safety.

10.6. ADVERSE EVENTS

10.6.1. Recording and Reporting Adverse Events

10.6.1.1. Adverse Event (AE)

An adverse event is any undesirable and unintended sign (e.g., an abnormal laboratory test result), symptom, or disease that occurred in a subject who was administered an investigational product, and it does not necessarily have to have a causal relationship to the drug used in the clinical study.

The principal investigator and investigator delegated by the principal investigator shall record all adverse events that occur during the clinical study. Adverse events have to be recorded using terms in the MedDRA® as much as possible, but if this is not possible, they should be recorded using the terms for the signs and symptoms observed by the principal investigator or investigator or reported by the subject.

Symptoms and signs that appeared in the subject prior to the screening should be recorded in the "Medical/Surgical History" section in the subject's CRF. All adverse events that appeared after administration of the investigational product should be recorded the adverse event section in the CRF, regardless of their relevance to the drug. The subject's pre-existing signs and symptoms of which their intensity, nature, or frequency has changed or the pre-existing diseases of which their names have changed after administration of the investigational product shall be considered and recorded as adverse events.

Adverse events shall be evaluated by the principal investigator and investigator delegated by the principal investigator. Adverse events that are recorded for the first time shall be recorded in the "Adverse Event" section of the CRF. Symptoms and signs of adverse events, actions taken in connection with the study drug, date and time of onset (if available), outcomes, course (i.e., continuous or intermittent), severity, seriousness, actions taken, and causal relationship to the study drug should be documented in the CRF. Details of dose changes and treatment information should be recorded in the appropriate pages of the CRF.

Adverse events previously recorded in the CRF and indicated as "ongoing" in the Outcome section should be reviewed in subsequent visits, if necessary. In the case that adverse events are resolved, records in the CRF should be completed. If the frequency and severity of adverse events increase during the study period, new records should be started in the adverse event section.

Besides the voluntary report from the subjects, ask the subjects in a manner not inducing to have a desired answer, such as "do you feel different since the last visit or administration?", as a consistent method to identify adverse events.

10.6.1.2. Adverse Drug Reaction (ADR)

It refers to any harmful and unintended reaction that occurred at a certain dose of the investigational product where a causal relationship to the investigational product is ruled out.

The causal relationship shall be evaluated with reference to the available information on the drug (e.g., investigator's brochure or a package insert of the drug).

10.6.1.3. Unexpected Adverse Drug Reaction

It refers to a reaction that shows a difference in the characteristics or degree of harm of the adverse drug reaction in view of the available information on the drug (e.g., investigator's brochure or a package insert of the drug).

10.6.2. Evaluation of the Severity of Adverse Events

The severity of adverse events shall be classified based on the following criteria in consideration of the maximal intensity.

- Mild: In the case that the subject can easily tolerate with the minimal discomfort without disturbing the normal daily life (or function) of the subject
- Moderate: In the case that it causes significant discomfort disturbing the normal daily life (or function) of the subject
- Severe: In the case that it makes the normal daily life (or function) of the subject impossible

10.6.3. Evaluation of the Causal Relationship of Adverse Events to the Study Drug

The causal relationship of adverse events to the investigational product shall be evaluated as 6 levels shown below, and the principal investigator or investigator delegated by the principal investigator shall describe his/her opinion.

- Definite relationship: In the case that an adverse event has a reasonable temporal relationship from the point of administration of the drug, and symptoms subside when the administration is discontinued and appear again when the administration is given
- Probable relationship: In the case that an adverse event has a reasonable temporal relationship from the point of administration of the drug, symptoms subside when the administration is discontinued, and symptoms cannot be explained reasonably based on known characteristics of the subject's clinical condition
- Possible relationship: In the case that an adverse event has a reasonable temporal relationship from the point of administration of the drug, but it may have possibly occurred due to the subject's clinical condition or study procedure/conditions
- Unlikely related: In the case that there is no reasonable relationship in terms of the temporal relationship between the adverse event and the drug
- Not related: In the case that an adverse event is clearly due to the subject's clinical condition or study procedure/conditions
- Unassessable: In the case that a judgment cannot be made because the information is insufficient or contradictory, and the information cannot be supplemented or verified

The causal relationship between the drug and the adverse event shall be evaluated considering the following:

- Temporal relationship: Is there a temporal probability between the drug administration and the adverse event occurrence?

- De-challenge: Did the adverse event disappear or improve when the drug administration was discontinued?
- Re-challenge: Did the adverse event recur or worsen when the drug administration was resumed?
- Other alternate causes: Are there other possible causes of the adverse event (e.g., past disease, present medical disease, concomitant medications, or other risk factors)?
- Pharmacological relationship: Is there a pharmacological relevance when referring to the mechanism of action of the drug, drug information documents (e.g., IB, product manual) and safety information of drugs in the same class?

10.6.4. Reporting Serious Adverse Event/Adverse Drug Reaction (AE/ADR)

It refers to an adverse event or an adverse drug reaction that occurred at a certain dose of the investigational product that one of the following applies:

- In the case that results in death or is life-threatening

  A life-threatening case refers to an emergency situation which might cause death if medical treatment is not given (e.g., hepatic necrosis requiring liver transplantation, anaphylactic shock requiring emergency resuscitation).

- In the case that requires hospitalization or prolongation of hospitalization

  Receiving medical care in an emergency room, not in an inpatient room, is also considered hospitalization at the investigator's discretion (e.g., acute allergic reactions).

  Hospitalization for the following are not considered as serious adverse events:

  - ✓ Routine treatment or monitoring that is not related to a worsening of the condition, such as examination for hospitalization or diagnosis during pharmacokinetic sampling or training for administration of the study drug
  - ✓ Hospitalization for scheduled treatment and surgery for a pre-existing condition that is not related to the indications of an ongoing clinical study and has not been deteriorated

- In the case that results in permanent or serious disability and dysfunction
- In the case that results in congenital anomaly or birth defect

  If the subject's partner becomes pregnant during the clinical study, it should be reported immediately to the clinical research associate (or staff member) of ImmuneMed Inc., but it is not a serious adverse event, and the miscarriage, birth of deformed baby or developmental disorder should be reported as serious adverse events.

- In the case that is made by other medically important decisions

If a serious adverse event occurs between the administration of the investigational product and the last visit, the principal investigator or investigator shall report it to the PV (or staff member) of ImmuneMed Inc. within 24 hours regardless of the relationship of the adverse event to the study drug.

Pharmacovigilance
Staff member: Yoon Won Kim
Address: #2-2, Bio-3, Chuncheon Bioindustry Foundation, 32, Soyanggang-ro, Chuncheon-si, Gangwon-do, Korea
Telephone: +82-33-241-1664, +82-10-2480-1664
Fax: +82-33-258-6553
E-mail address: ywkim@immunemed.co.kr

The report shall be submitted to the relevant site in accordance with the criteria of the Institutional Review Board of the relevant site where the serious adverse event occurred. If it is considered a serious adverse event is related to the administration of the study drug, it should be reported to the clinical research associate (or staff member) of ImmuneMed Inc. at any time even after the end of the study.

10.6.5. Follow-Up on Adverse Events

The principal investigator or investigator followed up on the subjects who experienced adverse events until the symptom subsided, the abnormal clinical laboratory tests returns to the reference range, or the observed changes could be explained to satisfaction.

10.7. BLOOD COLLECTION AND ANALYSIS FOR PHARMACOKINETIC EVALUATION

10.7.1. Specimens and Analytes

Depending on the dose group, the concentration of the following substance in the serum shall be analyzed:

- Concentration of hzVSF-v13

10.7.2. Blood Collection Method and Pre-processing and Storage Methods of Separated Serum

- Single-dose study
  - Blood collection will be performed at 1 d 0 h (pre-dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 24 (2 d 0 h), 36 (2 d 12 h), 48 (3 d 0 h), 60 (3 d 12 h), 72 (4 d 0 h), 96 (5 d 0 h), 120 (6 d 0 h), 144 (7 d 0 h), 168 (8 d 0 h), 336 (15 d 0 h), 504 (22 d 0 h), 672 (29 d 0 h), 840 (36 d 0 h), 1,176 (50 d 0 h), 1,512 (64 d 0 h), 1,848 (78 d 0 h) and 2,184 h (92 d 0 h; post-dose). At each time point, 5 mL of blood will be collected.
  - Rationale for blood collection time points
    Blood will be collected for a duration of 2,184 h (approximately 13 weeks after the administration), which is 3 times the expected half-life (approximately 30 days) based on preclinical study results.
  - Blood will be collected via venipuncture or a saline-locked angiocatheter inserted into the brachial vein. In the case of collecting blood using a saline-locked angiocatheter, approximately 1 mL of blood will be drawn and discarded, and approximately 5 mL of blood will be collected. Then, 1 mL of saline will be injected into the catheter to prevent coagulation of the blood.

- The collected blood will be immediately placed in a serum separate tube (SST) and stored at room temperature. After leaving it for at least 30 minutes, it will be centrifuged at 4℃ for 10 minutes at 3,000 rpm in order to separate the serum.
- Approximately 0.7 mL of the serum separated by centrifugation will be placed in tubes to have 3 samples and prepared for storage in a freezer.
- The prepared samples will be transferred to a freezer at not more than −70°C within 1 hour and stored until they are analyzed.
- One of the three frozen samples (back-up sample) will be stored at the Seoul National University Hospital Clinical Trials Center, and the other two will be sent to the analyzing institution through a specialized shipping company.

10.7.3. Analytical Method

See Drug Concentration Analysis Method.

10.8 BLOOD COLLECTION AND ANALYSIS FOR EXPORATORY EVALUATION

10.8.1 Samples and Substances for Analysis

When stability and pharmacokinetics for investigational product is decided respectively, at the maximal 10mL of blood collection can be performed for the subjects who already agreed upon the written consent form for the research of the epidemiology of the genetic variance. Also, exploraryly evaluate the change in the proportion of immune cells in the lymphocytes to the baselines in peripheral blood.

Blood collection timepoint: 5mL of blood is collected on screening day and day 92 after administrated, respectively.

10.8.2 Blood collection method and pre-treatment and storage methods for separated serum

5mL of blood is collected for whole blood, which is performed through saline-locked angiocatheter which is equipped in either venipuncture or brachial veins. When blood is collected using a saline-locked angiocatheter, take 1mL of blood first to be discarded then 5mL of blood is collected and 1 mL of saline is injected into catheter in order to prevent the blood coagulation .

5mL of collected blood should be contained in a container (EDTA TUBE) immediately and stored in freezing condition (below -70℃).

10.8.3 Analytical method

In case of large deviations of individual study drug effects, they can be explored through analysis, including genetype, if necessary. In this case, they are prepared in a separate result report.

10.9. ENDPOINTS AND ANALYTICAL METHOD

10.9.1 Safety Endpoints

1) Adverse events, such as subject and objective symptom

The investigator should record all adverse events that occurred during the clinical study. Also, adverse events have to be recorded using terms in the MedDRA® as much as possible, but if this is not possible, they should be recorded using the terms for the signs and symptoms observed by the investigator or reported by the subject. Signs and symptoms of adverse events, duration (start/end date), severity (mild, moderate, severe), causal relationship to the study drug, measures taken against adverse events, serious adverse event (yes/no), etc. shall be recorded in the CRF.

2) Vital sign, physical examinations, electrocardiography (12-lead ECG), clinical laboratory tests, immunogenicity test

The purpose of this clinical study is to evaluate the safety and pharmacokinetic characteristics, and this clinical study has only a small number of subjects assigned to each dose group, and the baseline values vary by subject. For this reason, strict statistical analysis of all subjects will not be performed.

The results of vital sign , physical examination, electrocardiography (12-lead ECG), clinical laboratory tests, and immunogenicity test will be reviewed comprehensively. Then, abnormalities of clinical laboratory test results will be evaluated for each subject, the clinical significance of the results will be recorded, and the relevance to the study drug will be reviewed.

- **Vital signs:** Blood pressure (systolic blood pressure and diastolic blood pressure), pulse rate and temperature shall be measured while maintaining a sitting position for at least 3 minutes without any sudden posture change.
- **Physical examination:** The investigator shall perform a physical examination at the scheduled examination time. During the screening tests, all signs and symptoms of physical examination shall be recorded in the case report form (CRF), and newly observed abnormalities or any changes to previously observed abnormalities (deterioration or improvement) in subsequent tests shall be recorded in the case report form (CRF).
- **Electrocardiography (12-lead ECG):** Besides the basic items, ventricular rate, PR interval, QRS, QT, QTc, etc. shall also be recorded in the case report form.
- **Clinical laboratory tests:**

Hematology	WBC with differential count (neutrophil [seg.], lymphocyte, monocyte, eosinophil, basophil), RBC, hemoglobin, hematocrit, platelet
Blood chemistry	Calcium, phosphorus, glucose, BUN, uric acid, cholesterol, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, γ-GT, CPK, LDH, creatinine, sodium, potassium, chloride, triglyceride, amylase, lipase
Urinalysis	Color, specific gravity, pH, WBC(s), nitrite, albumin, glucose, ketone, urobilinogen, bilirubin, occult blood with microscopy

- **Immunogenicity test:** Immunogenicity will be evaluated by confirming the production of antibodies against hzVSF-v13.
- **Urine drug test:** Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates (to be performed only at the screening)

- **Serology:** Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) (to be performed only at the screening)

10.9.2 Pharmacokinetic Endpoints

The actual blood collection time by subject will be used during the analysis of pharmacokinetic characteristics. If the measured concentration is lower than the lower limit of quantification (LLOQ), the actual blood collection has not been performed (not applicable), or the blood sample is missed (missing data), "<LLOQ," "N/A" or "MD" will be entered in the blood drug concentration data. A blood concentration–time pattern of the study drug will be shown as a graph in a linear or log/linear shape for each subject, and the mean blood concentration–time curve by dose group will be shown in the same way. The obtained data will be used to calculate the following pharmacokinetic parameters through a noncompartmental method by using Phoenix® (Pharsight, CA, USA):

1) Single-dose study:

C_{max}, AUC_{last}, AUC_{inf}, T_{max}, $t_{1/2}$, CL (or CL/F), and V_d (or V_d/F) of hzVSG v13

C_{max}	Maximum blood concentration after administration of a single dose
AUC_{inf}	Area under the blood concentration–time curve extrapolated to infinity after administration of a single dose. $AUC_{inf} = AUC_{last} + C_{last} / \lambda_z$
T_{max}	Time to reach the maximum blood concentration after administration of a single dose
$t_{1/2}$	Elimination half-life
CL	Clearance after administration of a single dose. CL = Dose / AUC_{last}
V_d	Volume of distribution after administration of a single dose. $V_d = CL / \lambda_z$

10.9.3 Statistical Analysis Method

The results of the safety and pharmacokinetic/pharmacodynamic assessments will be statistically analyzed as shown below at a significance level of 0.05 using software such as SAS® or SPSS® .

10.9.4 Subject Group to Be Analyzed

All subjects who were randomized, who received the drug administration, and who has evaluable pharmacokinetic results will be classified and analyzed. Demographic data will be analyzed for all subjects who have been randomized (intention-to-treat), and the safety assessment will be performed for subjects who have received the investigational product (hzVSF-v13 or placebo) at least once. The pharmacokinetic assessment will be performed for subjects who completed the clinical study as planned without any serious

protocol violation that may have an impact on the pharmacokinetic results (per protocol). However, information of drop-out subjects may be referenced for the pharmacokinetic assessment.

10.9.5 Demographic Information

Descriptive statistics (mean, standard deviation, etc.) will be obtained for all subjects and each dose group for basic demographic information of subjects, such as age, height, and weight.

10.9.6 Pharmacokinetic Assessment

Pharmacokinetic parameters will be obtained through a noncompartmental method using an appropriate and verified pharmacokinetics software (e.g., Phoenix WinNonlin® [Version 6.3 or higher; Pharsight, CA, USA]), and descriptive statistics (mean, standard deviation, median, maximum, minimum, etc.) will be obtained for each dose group.

10.9.7 Safety Assessment

With regard to the occurrence of adverse events, number of cases occurred, number of subjects who experienced adverse events, severity, seriousness and causal relationship to the study drug will be analyzed by treatment group using descriptive statistics and compared by applying the non-parametric method as needed.

The investigator will perform statistical analysis as needed for the items that are considered clinically significant.

10.10. STORAGE AND DESTRUCTION OF SAMPLES

Blood and urine samples collected for various clinical laboratory tests shall be stored and destroyed of at the place designated by Seoul National University Hospital Department of Laboratory Medicine. Besides, samples collected for pharmacokinetic analysis, immunogenicity analysis, etc. shall be stored and destroyed of in accordance with the management standards of APACE Co., Ltd. or Hallym University College of Medicine Laboratory.

11. RESEARCH ETHICS

11.1. TAKEN ACTION FOR PROTECTION OF SUBJECTS' SAFETY

The principal investigator or investigator shall take full responsibility for all medical decisions related to the clinical study.

If adverse events occur from after administration of the investigational product or after the final administration until the last visit, the principal investigator shall take action for appropriate medical treatment against any adverse events that occurred in subjects in the clinical study, including clinically significant laboratory test results. In the case that medical treatment is required for subjects' intercurrent diseases that have been notified to the principal investigator, the subjects have to be informed of such information.

The subjects have to be instructed to visit the hospital immediately in case of adverse events in order to recieve

the necessary tests which will be performed by the investigator, to receive treatment, and to be followed up until symptoms subside. In the case that serious adverse events occur during the clinical study, the obligations of the principal investigator, investigator, Institutional Review Board (IRB) and sponsor are as shown below.

Obligations of the principal investigator

The principal investigator has to immediately inform the sponsor of all serious adverse events, except for the ones specified in the protocol that an immediate report is not required, and submit a document including detailed information as an additional report. Afterward, a report has to be submitted to the Institutional Review Board (IRB) in accordance with the standards of the Institutional Review Board (IRB) of the site.

Obligations of the investigator

The investigator has to fully understand the expected adverse events and precautions for use that are stated in the protocol in advance, and report to the principal investigator in case of serious adverse events while conducting the clinical study.

Obligations of the Institutional Review Board (IRB)

The Institutional Review Board (IRB) has to notify the principal investigator of the required action through an expedited review if the serious adverse events reported by the investigator are serious adverse drug reactions.

Obligations of the sponsor

If the principal investigator or investigator reports serious adverse events, the sponsor has to attach a copy of the adverse event report submitted by the principal investigator or investigator to an adverse event report and submit the document to the Ministry of Food and Drug Safety immediately (if they are deemed to be suspected unexpected serious adverse reactions). In the case that the clinical study is conducted at multiple study sites, the relevant study sites have to be notified immediately.

11.2. EXAMINATIONS AND TREATMENT CRITERIA FOR SUBJECTS AFTER THE CLINICAL STUDY

The follow-up shall only be performed on the subjects who experienced adverse events after the end of the clinical study. In this case, all adverse events and changes in concomitant medications shall be recorded, and clinical laboratory tests shall be conducted if necessary. The subjects who experienced adverse events should be followed up until the symptom subsided, the abnormal clinical laboratory tests returns to the reference range, or the observed changes could be explained to satisfaction. In addition, the progress of adverse events should be reported to the staff member of ImmuneMed Inc.

11.3. OTHER ITEMS REQUIRED TO CONDUCT THE CLINICAL STUDY SAFELY AND SCIENTIFICALLY

This clinical study has been designed in consideration of the rights and welfare of subjects based on the Declaration of Helsinki. The principal investigator or the investigator shall explain the objective of this study and all possible results, and the subjects who voluntarily sign the informed consent form to participate in the clinical study will be selected as the subjects.

All investigators and participating study staff members have to fully analyze and understand the clinical study, and the principal investigator shall take action in advance, including countermeasures against unexpected adverse events, etc. and required reports as well as sufficient training for study staff members participating in the study. The clinical study shall be conducted in accordance with the ICH-GCP guidelines.

The conduct of this clinical study and storage of the clinical study-related records, etc. shall be based on the "Korean Good Clinical Practice for Drugs" announced by the Ministry of Food and Drug Safety, and this clinical study shall be monitored by a clinical research associate designated by the sponsor, ImmuneMed Inc.

11.3.1 Study Site

Equipment and professional personnel required for the clinical study should be prepared and the perfection in the preparation for the appropriate performance of this clinical study should be aimed.

11.3.2 Monitoring of the Clinical Site

The sponsor shall designate a clinical research associate who will be in charge of this study and will visit the study site at appropriate intervals, including the time point at which the first subject in each dose group completes the schedule up to 15 d and the time point at which the last subject in each dose group completed the schedule up to 15 d. During the monitoring visit, the clinical research associate will confirm the compliance with the protocol, current study progress reported by the principal investigator and investigator, consistency of data between hospital records and CRFs, adverse events, control of the investigational product, etc. For this, the principal investigator and investigator has to provide proper time and space for the monitoring visit made by the clinical research associate and give access to CRFs and hospital records.

11.3.3 Management of the Investigational Products

The clinical trial pharmacist shall sign the document verifying that the investigational products required for the study have been received, shall handle and store them as described in the "Code Name of the Investigational Product (or Generic Name of the Active Ingredient), Ingredients and Their Amounts, Formulation, etc." section, and shall administer the investigational product only to the subjects who participate in the study.

At the end of the study, the quantity of drugs used and returned has to be identical to the drug accountability

log; if there is any difference, the reason for such difference has to be explained. In order to guarantee the return of all unused investigational products, including all opened and unopened drug bottles and packages, the clinical trial pharmacist shall record and sign the final inventory/accountability logs.

11.3.4 Amendment to the Protocol

Any information in this protocol shall not be amended/revised unless there is mutual agreement after having a detailed discussion with the sponsor.

The amended/revised information in the protocol shall be applied to all subjects after obtaining an approval from the Institutional Review Board (IRB) as well as from the Ministry of Food and Drug Safety if the approval of Ministry of Food and Drug is required.

11.3.5 Inspection and Audit

For audits and inspections, the principal investigator and investigator shall comply with the requirements of the sponsor and the Ministry of Food and Drug Safety.

11.4. DATA PROCESSING AND DATA QUALITY ASSURANCE

The data management in this clinical study will be performed in accordance with the standard operating procedures of the Seoul National University Hospital Medical Research Collaborating Center and Clinical Trials Center as well as Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine. Other items not stated in the protocol will be performed in accordance with the ICH-GCP and KGCP regulations.

11.4.1 Source Data

Source data refers to any document, data and recordings, including medical records, electrocardiograms, clinical laboratory test results and drug accountability logs. The data collected during the study should be recorded in the appropriate source data. The data recorded in the screening/registration logs should include the subject identification number, screening date, reason for drop-out (in the case of drop-out), etc. All screened volunteers should be recorded in these logs.

The access to source data will be given in the event of the study monitoring, audit, review by the IRB, and inspection by regulatory authorities.

11.4.2 Recording in Case Report Forms and Verifying Source Documents

In this study, eCRFs developed using Medidata will be used. eCRFs will be recorded whenever data that need to be recorded are generated. If the data are not recorded until the finalization of the case, a proper reason for missing should be recorded. Data collection for all eCRFs will be done remotely based on source documents. The clinical research associate of the sponsor will periodically review and electronically sign eCRFs. The principal investigator will review the completeness and accuracy of eCRFs and electronically

sign them.

Data validation will be performed using a computer program (SAS) in order to verify whether there are logical errors, missing values, outliers, etc. for eCRFs of which the review sign is completed by the clinical research associate. Queries will be issued to the study site after making decisions on all errors found whether they are queries, and the site will correct eCRFs after checking the original data.

Even after computerization of all data, source documents and eCRFs will be retained to allow the verification of data by the relevant government agencies, IRB, etc. when requested. In addition, the investigator will provide normal ranges or reference values to other appropriate documents, such as eCRFs, prior to the initiation of the clinical study in order to use them for verification and validation of computerized records.

11.4.3 Data Entry Process

In this study, eCRFs will be used. All information recorded in eCRFs is based on the source document of the subjects and eCRFs of all subjects who have signed the informed consent form shall be completed. Data in eCRFs are entered through a database system developed using Medidata, and the data entry process is performed according to the SOP of the study site. Since complete pharmacokinetic data are generated after completion of eCRF entry, pharmacokinetic data will be excluded from the database system entry items. The principal investigator will review the completeness and accuracy of eCRFs and electronically sign them.

11.4.4 Storage of Research Documents

In accordance with the KGCP, essential documents required to be retained should be retained for 3 years from the date of investigational product approval. The retention period may be extended if the Minister of Food and Drug Safety orders or if the sponsor considers it is necessary.

In relation to this study, the original data are regarded as data on the Medidata server, and these data shall be kept at the Department of Clinical Pharmacology and Therapeutics, Seoul National University Hospital. If the sponsor wants to have access to the data, they may visit Seoul National University Hospital and to have access. In this case, Department of Clinical Pharmacology and Therapeutics shall grant authorization to have access. Even if Department of Clinical Pharmacology and Therapeutics no longer continues the Medidata program, authorization to have access to the data related to this study will remain on the Medidata server. In addition, electronic case report forms and audit trails will be converted into PDF files, which will then be sent to the sponsor via e-mail in order to archive.

11.4.5 Data Quality Assurance

The initiation meeting with participation of the investigators and the sponsor will be held prior to the

beginning of the clinical study. At this meeting, the protocol and the study conduct method, case report form completion method, sample collection method and pre-treatment method will be discussed in detail. The clinical research associate will monitor in accordance with the monitoring plan.

The study coordinator and clinical research associate will double check all data recorded in case report forms. If any abnormality is found, it will be compared to source documents. Data of case report forms should be entered into the database system using the single-entry method.

The list of queries for unresolved queries should be resolved with the investigators through the clinical research associate. The database shall be modified based on the signed query resolution.

Once data entry is confirmed, the database system shall be locked.

11.4.6 Data Security

All documents, such as source documents and eCRF obtained through the study, have to be retained securely, and the investigators shall not disclose such information without the sponsor's consent.

Since anonymity of the subjects has to be guaranteed, all documents shall use subject numbers and initials instead of names of the subjects. Any documents that may identify the subjects shall be retained securely by the investigator.

11.5. CONFIDENTIALITY AND PUBLICATION OF STUDY RESULTS

All information obtained during the clinical study is proprietary intellectual assets of the sponsor; therefore, the investigators and other persons related to the clinical study have to strictly maintain the confidentiality of such information.

12. REFERENCE

13. ATTACHMENTS

Attachment 1. Subject Information Sheet/Informed Consent Form for Participation

Attachment 2. Subject Recruitment Advertisement

Attachment 3. Name and Title of investigators and Clinical Trial Pharmacists

Attachment 4. Clinical Study Compensation Policy

Attachment 5. Subject Information Sheet for Collection of Human-Derived Materials

Attachment 6. Informed Consent Form for Research on Human-Derived Materials

Attachment 7. Informed Consent Form for Release of Information on Pregnancy